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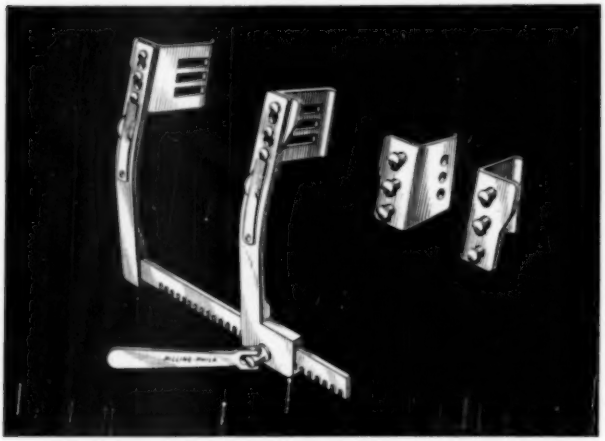

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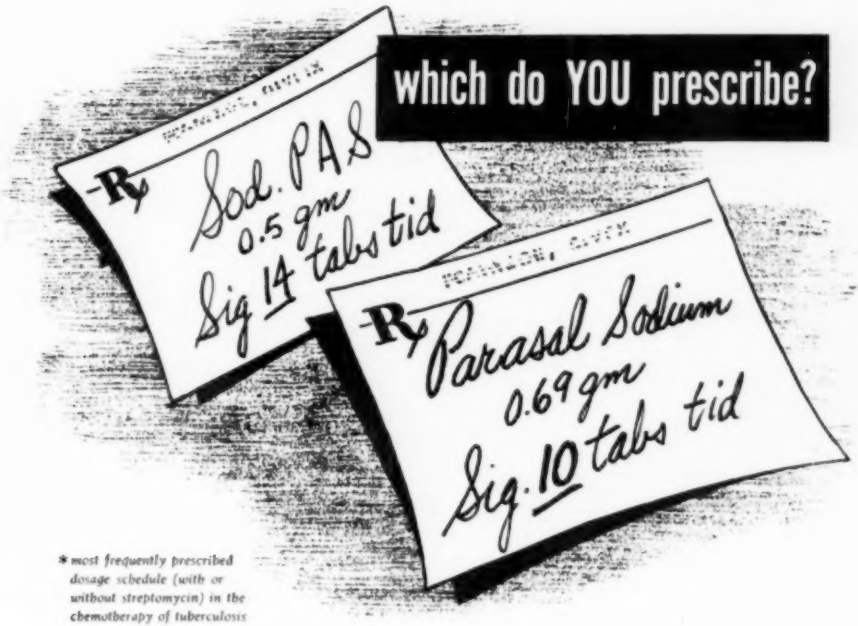

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THE AMERICAN REVIEW
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BOECK'S SARCOID[1]

A Review Based upon a Clinical Study of Fifty-two Cases

EDGAR ALSOP RILEY

(Received for publication April 20, 1950)

INTRODUCTION

This study of Boeck's sarcoid is based upon 52 cases of generalized sarcoidosis seen at Bellevue Hospital between 1939 and 1949. The average length of follow-up on the entire group has been four years and eight months. This average would have been considerably higher except for the fact that 6 patients were lost from follow-up after periods of less than six months. The longest follow-up has been nineteen years.

Because the etiology of this disease remains obscure and because its protean manifestations may include involvement of almost every organ of the body, sarcoidosis has aroused widespread interest, both in this country and abroad. This interest is not confined to one branch of medicine, but is shared by the internist, chest specialist, pathologist, roentgenologist, dermatologist, ophthalmologist, and otolaryngologist. The literature in recent years has reached unbelievable proportions. Much of it is redundant and repetitious. It was thought, however, that a study of a large and relatively well-studied series of cases would prove a valuable contribution. No attempt has been made to review the entire literature on sarcoidosis. The most complete and exhaustive recent review is that published by Freiman (8). Other excellent reviews are those by Pinner (9), Longcope (10), Rubin and Pinner (11), Snapper (12), Michelson (13), and Curtis and Grekin (14).

DESCRIPTION OF MATERIAL

These 52 cases do not represent the exact number of patients with this disease seen during this ten-year period. Several other cases of sarcoidosis are not included because of incomplete clinical data. Thirty-three of these patients at one time or another were on the Chest Service; the remainder were scattered throughout the various other services of the hospital. Since many of these patients have been followed over a period of years by various New York City Department of Health chest clinics, we are particularly indebted to the Bureau

[1] From the Bellevue Hospital Chest Service, New York, New York.

of Tuberculosis for its cooperation in this study. As far as can be determined, although several of these cases may have been included in Reisner's series (1), only 2 have been previously reported individually (2, 3, 4, 5). The clinical findings of sarcoidosis were substantiated by histologic examination of either autopsy or biopsy material in 44, or 85 per cent, of the 52 cases. The remaining 8 patients, 15 per cent of the total number, either signed out of the hospital against advice before biopsy could be performed, or were seen in a phase of the disease when biopsy material was not readily available. Although some writers believe that the diagnosis of sarcoidosis cannot be made without confirmatory histologic evidence and although it is recognized that this evidence is highly desirable, in certain instances the diagnosis can be made on the basis of clinical, laboratory, and roentgenographic findings without morphological confirmation. We have had no experience with the use of diagnostic skin tests with antigen made up from sarcoid material such as was first proposed by Williams and Nickersen (6) and later by Kveim (7).

HISTORICAL BACKGROUND

The historical background of Boeck's sarcoid has been extensively reviewed by others (15, 16) and need not be developed in great detail. Nevertheless, a brief review enables one to understand more clearly in what manner the present concept of the disease arose. The early history of sarcoidosis is particularly confusing. One factor contributing to this confusion has been the bewildering nomenclature applied to this disease at various times (table 1). The majority of these terms fortunately have fallen into disuse. In this country the terms sarcoidosis, Boeck's sarcoid, or simply sarcoid are employed most frequently and usually interchangeably. In the foreign literature the term benign lymphogranulomatosis seems to be most popular. None of these terms is completely satisfactory but general usage probably favors retaining the name sarcoidosis. This term was first coined by Boeck in 1899 (17) because of the fancied resemblance of the epithelioid cellular response to sarcomatous cells.

The second factor contributing to the confusion surrounding sarcoidosis is that the varying manifestations of the disease were initially described by various authors as separate diseases. The realization that they were different aspects of the same disease developed only gradually. Hutchinson (18) is generally credited with having presented, in 1875, the first gross morphological description of the skin lesions of this disease. In 1888 Mickulicz (19) published the description of the syndrome of parotid and lacrimal gland enlargement which first bore his name and which only recently has been recognized in certain instances to be a manifestation of sarcoidosis. The following year, Besnier (20) described as a new clinical entity a case of lupus pernio, but it was not until 1917 that Schaumann (21) recognized these skin lesions as the dermatological manifestations of a generalized disease which he called benign lymphogranulomatosis. The first mention of the disease in the American literature was by Osler (22), who in 1898 published a case report of a young Negro female with lacrimal and parotid gland enlargement, splenomegaly, and generalized adenopathy, and

who later in the course of her disease developed extensive tuberculosis. Although the diagnosis of sarcoidosis was not confirmed by histologic examination, the clinical course and findings in retrospect were very characteristic of sarcoidosis. It was in the following year that Boeck, as has already been mentioned, described the histologic features of the disease and considered it to be most probably of tuberculous etiology. In 1902 Keinboch (23) described the cystic lesions of the extremities, and two years later Kreibach (24) associated these changes with lupus pernio. In 1909 Heerfordt (25) described the clinical manifestations of Heerfordt's disease or uveoparotid fever, and in 1915 Kuznitsky and Bittorf (26) reported a case with visceral and pulmonary involvement. In 1919 Jungling (27) coined the cumbersome term osteitis tuberculosa multiplex cystica for the

TABLE 1

Nomenclature Disguising Sarcoidosis

Hutchinson's disease
Mortimer's disease
Tenneson's disease
Besnier's disease
Besnier-Tenneson's disease
Boeck's disease
Besnier-Boeck's disease
Schaumann's disease
Besnier-Boeck-Schaumann's disease (or syndrome)
Jungling's disease
Hutchinson-Boeck's disease
*Mickulicz disease (or syndrome)
Osteitis tuberculosa multiplex cystica
Noncaseating tuberculosis
Lupus pernio
Multiple benign sarcoid of the skin
Benign lymphogranulomatosis
Miliary (or disseminated) lupus
Uveoparotid fever

* In some instances.

lesions in the extremities which were formerly also known as Jungling's disease. When in 1936 Bruins Slot (28) suggested that uveoparotid fever was the same disease as sarcoidosis, the present concept of the disease was generally agreed upon.

PATHOLOGY

The pathological changes in Boeck's sarcoid are well known and have been described in detail by many authors. In brief, the basic lesions are granulomatous epithelioid cell tubercles which may completely replace the normal architecture of the organ in which they appear. These tubercles, found in association with giant cells of both the foreign body and Langhans' type, were present in biopsy or autopsy material from all 44 cases in this series in which histologic confirmation of the clinical diagnosis was obtained. A round cell response is not

uncommon and was present in 25, or 57 per cent, of the cases. A mild polymorphonuclear cell infiltration was present in 3 cases and a slight eosinophilic infiltration was described in one. Nonspecific necrosis is not incompatible with the diagnosis and was noted, usually to a slight degree only, in 11, or 25 per cent, of the cases. Inclusion bodies first described by Wolbach (29) in 1911 were present in 7, or 16 per cent, of these cases. These bodies were of two types: the asteroid inclusion body, and the doubly contoured deep-staining conchoid body later described by Schaumann in 1941 (30). The nature of these bodies and their significance is not known. Although formerly thought to be associated only with sarcoidosis, it is now recognized that they are nonspecific and occur in other diseases such as leprosy, lupus erythematosis, and occasionally tuberculosis.

It is generally thought that in certain instances these lesions may be reversible and regress without any demonstrable residuals. In some instances they may persist unchanged for many years. In one patient, F. V., a lymph node biopsy showed essentially the same pathologic changes demonstrated in a previous biopsy eleven years earlier. Calcification does not occur except occasionally in the Schaumann conchoid bodies. If the lesions do not regress spontaneously, they may heal through hyalinization and fibroblastic proliferation with fibrous tissue formation. This feature was noted in 26, or almost 60 per cent, of the cases. The end stage is represented by a wholly nonspecific area of fibrosis which, depending upon its anatomical location, may result in irreversible functional damage.

The presence or absence of caseation necrosis is the one definite criterion which may be used to distinguish between Boeck's sarcoid and tuberculosis on purely morphologic grounds. If one postulates that the two are separate diseases, the finding of caseation makes the diagnosis of Boeck's sarcoid alone untenable. One patient, who did not develop clinically active tuberculosis, showed questionable minimal caseation necrosis on biopsy specimen. This finding was not substantiated on later autopsy examination. In view of the clinical course of this patient and because of lack of corroborating evidence, the diagnosis of sarcoidosis is still valid. The difficulty in differentiating between nonspecific and minimal or early caseation necrosis in some instances is well known. With the exception of this case, the absence of caseation was uniform among those patients in whom tuberculosis was not a complicating factor.

It is important to remember, as Pinner (31), among others, has stated, that the morphologic appearance is nonspecific and that a sarcoid-like reaction may be caused by a number of different etiologic agents. The term sarcoidosis should be reserved for the generalized disease with evidence of widespread disseminated foci in which there must be a close correlation between the clinical findings and the evaluation of pathologic material.

CLINICAL MATERIAL

Although Boeck's sarcoid has been reported in every age group, it is primarily a disease of young adulthood. It is admittedly difficult to date the onset

of sarcoidosis in those asymptomatic patients in whom the disease is first demonstrated by findings on a routine physical examination or chest roentgenogram, or when it is discovered as a coincidental finding in association with another disease. In this series, if the onset is considered to be the time when the diagnosis was established or when symptoms developed, 29 patients were in the third decade of life (table 2). This finding coincides with other comparable groups (1, 32, 33, 34).

TABLE 2

Age Incidence

AGE GROUP	NUMBER	PER CENT
10 to 20	9	17
20 to 30	29	56
30 to 40	8	15
40 to 50	6	12
Total	52	100.0

TABLE 3

Incidence by Sex and Race

	NUMBER		PER CENT	
Negro female	28		54	
Negro male	13		25	
Total Negro		41		79
White male	8		15	
White female	2		4	
Total white		10		19
Puerto Rican female (Negroid)	1		2	
Total Puerto Rican		1		2
Total	52	52	100	100

A high frequency of this disease has been noted among the Nordic races, particularly in Scandinavia where several large series have been reported. Although certain authors, such as Dimsdale (35), feel that there is no particular preference for race or sex, it is now generally agreed that, in this country at least, the disease appears most frequently in the Negro race and that there is a higher incidence among females than males. Over 50 per cent of the patients in this series were Negro females, and the total incidence among Negroes reached almost 80 per cent (table 3). Somewhat surprisingly, there was only one Puerto

Rican in the group, and this patient showed pronounced Negro racial characteristics. The majority of the Negroes were American born, but several were immigrants from the British West Indies. The 10 white patients were of varying racial backgrounds.

The realization that this disease shows a definite racial preference has developed within the last few years. As recently as 1937, Jordon and Osborne (36) commented on the rare incidence in the Negro race. The early reports from the South, such as Longcope's (10), were perhaps weighted because of the higher incidence of the Negro population in that area, but 86 per cent of Reisner's group from New York City were Negroes, as were 42 per cent in Garland's series from San Francisco. The recent Army experience has also helped to clarify the racial distribution. At the Conference on Sarcoidosis, held on February 11, 1948 under the auspices of the National Research Council, Division of Medical Sciences, it was reported by the Army Institute of Pathology that from the material gathered on this disease during the war the estimated rate in Negroes was sixteen times the estimated rate in white soldiers. The higher incidence of the disease in females has been corroborated in all other comparable series. No satisfactory explanation has been given to explain this racial, sexual, and age predominance.

The incidence of significant tuberculous contacts has been low in this series. Among 47 cases in which it was specifically determined, 6, or 13 per cent, gave a positive history. In several of these the intimacy of contact was not determined. Most series have shown a similar low incidence, although Hagn-Meincke, in a review of 26 cases (37), reported a history of contact in one-half of his patients. There have been no instances of the disease occurring in siblings in this group. The past histories were essentially noncontributory. Nine patients gave a history of treated syphilis, there were 5 cases of fairly well-documented rheumatic fever with and without cardiac involvement, two histories of previous nonspecific pleurisies, and one history of an unexplained pleurisy with effusion, presumably on a tuberculous basis. Otherwise these patients were singularly free from previous illnesses, a fact best explained by the relatively early age incidence.

SYMPTOMATOLOGY

One of the most characteristic features of sarcoidosis noted by many writers has been the lack of correlation between the severity of symptoms and extent of involvement. This disparity has almost diagnostic significance, particularly in the evaluation of pulmonary lesions. In this series, however, only 9, or 17 per cent, were completely asymptomatic. The remaining 43 patients had symptoms at one time or another which were directly referable to their disease. These symptoms, although there were dramatic exceptions, appeared to be in proportion to the severity of involvement (table 4). It will be noted that the majority of these complaints were referable to the chest, which is not surprising if the high incidence of pulmonary involvement is considered. Ten patients complained of blood-streaked sputum, probably on the basis of the bronchiectasis

which is present not infrequently, secondary to the pathological pulmonary changes. In several instances, however, this complaint was not substantiated by the observation of blood-streaked sputum during the period of hospitalization, so perhaps is open to question. In 2 instances, there were episodes of foul sputum, the result of superimposed infection. Weight loss was noted in over 50 per cent of the symptomatic group. Although fever was a subjective complaint of 6 patients, 26, or 50 per cent, of the entire group ran a febrile course during their period of hospitalization. This was of mild degree in all cases but 2. Wheez-

TABLE 4

Symptomatology

Asymptomatic	9	17.4 per cent
Symptoms	43	82.6 per cent

SYMPTOMS	NUMBER	PER CENT*
Sputum	28	65
Occasional streaking	10	
Occasionally foul	2	
Cough	27	63
Weight loss	22	51
Shortness of breath	18	42
Weakness and/or easy fatigue	12	28
Chest pain	9	21
Diminished vision	7	16
Fever	6	16
Wheezing	6	14
Anorexia	6	14
Night sweats	5	12
Skin eruption	4	9
Palpable glands	4	9
Miscellaneous	20	49

Abdominal pain	3	Ocular pain	1
Nausea	2	Asthma	1
Swelling of fingers and toes	2	Substernal tightness	1
Menstrual irregularities	2	Facial weakness	1
Photophobia	2	Headache	1
Hoarseness	1	Chills	1
Shoulder pain	1	Subcutaneous nodules	1

* Of the symptomatic group only.

ing, most probably due to a concomitant bronchitis, was noted by 6 patients. It is difficult to ascribe the group of miscellaneous complaints directly to sarcoidosis in certain instances, but they were a prominent enough part in the over-all clinical picture to deserve mention. Some of them, such as abdominal pain, nausea, and hoarseness, may be explained on the basis of pressure symptoms from regional adenopathy.

In remarking upon these symptoms, it should be remembered that these patients represent a hospitalized group, in whom one would expect the symptoms

to be more severe than in a cross-section, nonhospitalized group of patients with sarcoidosis. In addition, it has been suggested that sarcoidosis may run a more severe course in the Negro than in the white race (38).

CLINICAL FINDINGS

Since Boeck's sarcoid is a chronic protracted disease in most instances, with frequent episodes of remissions and exacerbations, the clinical findings at any one time do not give a true picture of the disease. The patients in this series have been followed for a period of years and for this reason it has been possible

TABLE 5

Distribution of Lesions as Determined Clinically

	NUMBER OF PATIENTS		PER CENT	
Adenopathy		52		100
Generalized peripheral	31		60	
Discrete	14		27	
Mediastinal	44		85	
Bronchopulmonary	44		85	
Right paratracheal	22		42	
Lungs		45		87
Splenomegaly		21		40
Hepatomegaly		19		37
Skin		13		25
Ocular		15		29
Uveal tract	12			
Lacrimal glands	5			
Fundus	1			
Osseous		7		13
Extremities	7			
Nasal bones	2			
Long bones	1			
Parotids		2		4
Miscellaneous				
Tonsils		1		
Bronchus		1		
Subcutaneous tissue		1		

to obtain a fairly true picture of the clinical features. The distribution of lesions as determined clinically is presented in table 5.

The most constant finding was lymphadenopathy. This was noted in all patients in this series at some time during the course of the disease, and has been a consistent finding in other series. The enlarged nodes were firm, discrete, and were usually not tender. It has been shown (39), however, that the involved nodes need not be palpably enlarged. Indeed, Garland (32) advocates routine exploration of the mesial end of the right supraclavicular fossa to obtain an involved but not palpable upper anterior mediastinal node for biopsy in those cases in which there is no peripheral adenopathy. In 31 patients the peripheral

adenopathy was generalized, involving three or more groups of nodes. In the remaining patients the involvement was limited to a single node or to one or two groups, without apparent predilection for any one site or combination. Forty-four cases showed roentgenographic evidence of mediastinal node enlargement, usually symmetrical and always bilateral. In 22 instances this was accompanied by enlargement of the right paratracheal or tracheobronchial node, a point thought to be of significance by some but actually explained by the presence of a large right tracheobronchial node without the presence of a corresponding node on the left (40). The true incidence of mediastinal node involvement on pathologic examination is probably higher because of the roentgenographic difficulty in interpreting borderline cases of hilar adenopathy, especially when the hilar area may be obscured by extensive pulmonary parenchymal disease.

Chest roentgenograms were available on all patients and pulmonary involvement was noted in 45, or 87 per cent, of these cases; the changes are discussed elsewhere. Splenomegaly and hepatomegaly were the next most common features present in 21, or 40 per cent, and in 19, or 37 per cent, of the patients, respectively. This incidence of presumptive involvement is naturally considerably lower than that found on pathologic examination (41). Skin lesions were found in 13, or 25 per cent, of the patients. This incidence is somewhat lower than in the series reported by Longcope (10) and Reisner (1). Dermatologists and others such as Schaumann (39) have laid great stress on the disappearance of the skin lesions simultaneously with the development of active tuberculosis, stating that it implies a tuberculous etiology of this disease. Of the patients with skin lesions in this series who have developed active tuberculosis, no change in the skin lesions has been noted which was not consistent with the natural course of this manifestation. As recently suggested by Bjornstad (42), it is thought that the regression, if it occurs, is purely coincidental. In several of these patients no changes took place, and further skin lesions continued to appear following the onset of overt tuberculosis.

Ocular involvement occurred in 15, or 29 per cent, of the cases. The most common site of involvement was the uveal tract, followed next in order by lacrimal gland enlargement. One patient developed a granulomatous lesion in the fundus. Osseous lesions, most commonly present in the extremities, were noted in 7, or 13 per cent, of the patients. This does not represent the true incidence of this site of involvement, since Schaumann (43) and others have shown that pathologic changes may occur without roentgenographic abnormalities and that, in addition, in the early stages these changes may be reversible. The low incidence of parotid gland involvement is probably best explained by failure during the history taking to inquire specifically about past involvement of these glands, or to the tendency to ascribe enlargement to other diseases such as mumps. One case of tonsillar sarcoidosis was proved by biopsy. Only one patient in this series had a tonsillectomy and, if more tonsillectomies had been performed, one might expect the incidence to have been higher. Schaumann (39) has found evidence of tonsillar involvement by sarcoid in 21 cases

of generalized sarcoidosis although the gross appearance of the tonsil was normal. Endobronchial involvement has been reported (44) and there was one case of presumptive bronchial sarcoidosis demonstrated on bronchoscopy, but unfortunately not proved by tissue examination.

Among the pertinent miscellaneous findings are included clubbing of the distal phalanges in 4 patients, which was associated with extensive osseous changes in one, pulmonary fibrosis in 2, and was present as an isolated finding in the fourth. Keloid formation over the site of operative procedures was present in 4 patients, 3 of them Negroes, but is of doubtful significance. Two patients developed peripheral nerve weakness. One had an unexplained transient foot drop. The second suffered from a temporary facial nerve paralysis associated with a progressive iridocyclitis but without demonstrable parotid gland involvement. Peripheral nerve weakness is not an uncommon finding in this disease (45) but facial nerve involvement is almost always accompanied by parotid gland enlargement, one of the features of uveoparotid fever (25). One patient developed skin lesions characteristic of erythema multiforme; and another, lesions suggestive of erythema nodosum. Lofgren (46), in reviewing a series of cases of erythema nodosum found that approximately 3 per cent were associated with sarcoidosis. Kerley (47, 48) has also found an association between the two diseases. The possible significance of the coexistence of the two diseases has not been stressed in this country, probably because of the relative infrequency of erythema nodosum and erythema multiforme. Their association, however, together with the high incidence of eosinophilia in sarcoidosis, has been considered evidence in favor of the theory that sarcoidosis is some form of allergic manifestation. This theory is difficult to reconcile with the generally accepted concept that most patients with sarcoidosis are usually anergic. The following case report is included because of the interesting association (which admittedly might be purely coincidental) with acute rheumatic fever and erythema nodosum.

Case Report

Case 42. G. O., a 23-year-old Puerto Rican female, was first admitted to Bellevue Hospital on February 1, 1947 with a history of fever and migratory joint pains of one week's duration, involving the interphalangeal joints, wrists, elbows, and knees. The illness was accompanied at the onset with coryza and cough.

Physical examination revealed a moderately febrile young female in no distress. No peripheral lymphadenopathy was present. Spleen and liver were not enlarged. There was sinus tachycardia and the second pulmonic sound was louder than the second aortic sound. The pharynx was injected; the lungs were clear. There was slight swelling, redness, and tenderness of the left wrist and left knee. A patellar click was elicited on the left. An erythematous rash, noted over the left leg, was described as suggestive of erythema nodosum.

Laboratory studies revealed a normal urine and blood count. A serologic test for syphilis was negative. The erythrocyte sedimentation rate was 49 mm. per hour. The serum proteins were 6.5 gm. per 100 cc. with an A/G ratio of 4.1/2.4. A chest roentgenogram showed enlarged parahilar and right paratracheal nodes with an extensive, diffuse, mottled bilateral parenchymal infiltration. Roentgenograms of the hands, knees, and wrists were negative. The tuberculin test was negative up to 1.0 mg. of Old Tuberculin. The electrocardiogram showed a normal sinus rhythm with a normal P-R interval.

On symptomatic therapy the patient gradually improved. A follow-up erythrocyte and leukocyte count showed an 11 to 14 per cent eosinophilia. The joint symptoms improved on administration of salicylates. Blood culture was negative. The patient was discharged on March 11, 1947 with the diagnosis of rheumatic polyarthritis.

The patient was readmitted on May 1, 1947 with the history of persistent afternoon fever since discharge, weakness, shortness of breath, slight cough, and weight loss. Physical examination was essentially unchanged except for the finding of an enlarged, firm, nontender right supraclavicular node. Inconstant sibilant rales were also heard in the left interscapular area. There was essentially no change on the chest roentgenogram. Laboratory studies were essentially normal except for an elevated sedimentation rate. Many sputum concentrates and several gastric aspirates were negative on smear and culture for acid-fast bacilli. The tuberculin skin test was negative up to .01 mg. of OT. The serum proteins were 6.2 gm. per 100 cc. with an A/G ratio of 4.5/1.7; an electrocardiogram was normal.

On May 29, 1947, the right supraclavicular node was biopsied and the report of the pathologist is as follows: "The normal architecture is replaced by bundles of cells with pale, large nuclei arranged in irregular masses. A few collections of lymphocytes and plasma cells can be seen. Occasionally a large multinucleated giant cell composed of the large pale cells can be seen. There is no evidence of necrosis. On acid-fast stain, no acid-fast bacilli are seen." A guinea pig inoculated with the node showed on autopsy no gross or microscopic evidence of tuberculosis.

The patient's course was afebrile and asymptomatic. She was transferred to the Municipal Sanatorium at Otisville for a period of sanatorium care on August 28, 1947.

Physical examination showed no significant changes except that at this time there were palpable nodes in the left cervical, right axillary, and in both inguinal areas. No significant changes appeared on serial chest films. Roentgenograms of the hands and feet were negative. Her sputum was negative for acid-fast bacilli on smear and culture. The tuberculin skin test was negative up to 1.0 mg. of OT. She was afebrile and her cough became minimal, but slight dyspnea on exertion persisted. It was believed that the lymph nodes showed regression. She was discharged on October 26, 1947.

Serial roentgenograms in 1948 showed regressive changes. On May 7, 1948, she was admitted to another hospital at which time biopsy of a right inguinal node revealed changes again consistent with Boeck's sarcoid. Persistent bilateral posterior apical rales and breath-sound changes were noted posteriorly. At this time her spleen was easily palpable, and in the roentgenogram the liver appeared enlarged. The erythrocyte sedimentation rate was 41 mm. per hour. Bone marrow studies showed an increase in the granulocytes, eosinophilia, and a slight increase in plasma cells. By January 3, 1949, the spleen was no longer palpable. On the patient's last visit on May 16, 1949, she felt well and was asymptomatic. A chest film on May 2, 1949, showed definite decrease in the extent of the infiltration previously reported in both lung fields.

Because of the frequency of pulmonary involvement, the cardio-respiratory findings are of special interest. Exclusive of those patients with cardiovascular disease of known cause, the only consistent cardiac finding was tachycardia, which was present in 21, or 40 per cent. Accentuation of the pulmonic second sound was noted in 16 patients. Although not an unusual finding in this age group, in several patients with pulmonary lesions it was markedly accentuated, suggesting some degree of pulmonary hypertension. Systolic precordial and pulmonic murmurs were present in a few instances.

The disparity between the severity of the disease and the symptoms applies in many instances to the physical findings on auscultation and percussion of the chest. Roentgenograms showed that rales were present in 25 of the patients with

pulmonary changes. These were usually scattered, although in 4 patients they had a basal distribution and in one instance were localized over a single lobe. Scattered wheezes and rhonchi were heard intermittently in 14 patients. Abnormal breath-sound changes were noted occasionally. None of these signs could be explained by any superimposed transient respiratory infection. Clinical findings consistent with emphysema were noted only twice. This freedom from physical signs, before complicating secondary changes have developed, is generally attributed (8, 49) to the distribution of the lesions in the early stages along the lymphatics and in the interstitial tissues of the lung.

LABORATORY FINDINGS

A summary of the pertinent laboratory data is presented in table 6. Many of the abnormal findings were not present on repeated examinations but were

TABLE 6

Pertinent Laboratory Studies

TEST OR PROCEDURE	NUMBER OF PATIENTS	RESULTS	NUMBER	PER CENT
Serologic test for syphilis	44	Positive	5	11
Hemoglobin and/or erythrocyte determination	44	Anemia	11	25
Total leukocyte count	46	Leukocytosis	4	9
		Leukopenia	10	22
Differential leukocyte count	45	Eosinophilia	11	24
		Monocytosis	7	16
		Granulocytopenia	4	9
Sedimentation rate	32	Elevated	25	78
Serum proteins	37	Elevated globulin	25	68
Alkaline phosphatase	15	Elevated	7	47
Cephalin flocculation	11	Positive	5	45
		Equivocal	3	27
Serum calcium	11	Elevated	2	18
Serum phosphorus	11	Elevated	2	18

observed only at one time during the course of the disease. They could not be correlated with any particular phase, as has been the case in other series. The 2 patients in whom high values for serum calcium occurred had renal damage unassociated with sarcoidosis. As far as can be determined, the frequency of a positive cephalin flocculation test has not previously been noted. Elevation of the serum globulin with a normal serum albumin, present in 67.5 per cent of the patients in whom this determination was done, has been considered one of the most characteristic features of the disease (50). The significance of the majority of these abnormal findings has never been entirely clear. Bone marrow studies were normal in 3 patients, and in a fourth (G. O.) showed findings already mentioned. The thymol turbidity test, done in 2 instances in which the cephalin flocculation test was positive, was also positive in both patients. In one of these 2 patients the bromsulfalein test showed 100 per cent dye retention. All other studies were either unrelated or normal.

Bacteriologic studies were largely directed toward attempts to recover tubercle bacilli. In 40 patients repeated acid-fast stains on specimens of sputum and gastric aspirates were negative except in 4 instances. In all 4 of these cases, however, subsequent smears and concomitant and subsequent cultures for tubercle bacilli were negative. Thus, it is believed that the positive findings in these 4 instances represented either laboratory errors or the presence of nonpathogenic acid-fast bacteria other than tubercle bacilli. Acid-fast stains reported in 39 instances on biopsy or autopsy material were all negative, as were repeated gastric and sputum cultures for tubercle bacilli performed on 30 patients. Guinea pig inoculation of sputum and biopsy or autopsy material were negative in 8 patients. Acid-fast smears of nasal scrapings were negative in 2 patients; lymph node or biopsy tissue culture for tuberculosis was negative in 3 patients; and culture of pleural fluid for tubercle bacilli was negative in one patient who had repeated spontaneous pneumothoraces, one of which was accompanied by a hydrothorax.

These findings substantiate the well-established historical fact that in this disease, unless complicated by tuberculosis, tubercle bacilli have never been unequivocally demonstrated by the presently accepted methods of culturing the organism.

Routine bacteriologic studies of the sputum and nasopharynx revealed only the normal bacterial flora. In 9 of 12 patients, gastric aspirate and sputum cultured for fungi were negative. The 3 other cases revealed *Monilia* in 2 patients and an unidentified yeast in the third. These were thought to be saprophytes and of no pathogenic significance, although a fungus etiology for this disease has been suggested (51).

Miscellaneous studies included angiograms in one patient and bronchograms in another, with normal findings on both occasions. Bronchoscopy was performed in 4 cases. In one instance already mentioned, a granulomatous endobronchial lesion was noted. In the second patient the findings were negative, and in the remaining 2 patients some reddening of the bronchial mucosa was apparent. In addition, in one of these patients with bilateral hilar adenopathy, external pressure on both main bronchi was evident, presumably from enlarged mediastinal nodes. This finding, as pointed out by Chamberlain (52), is rare in sarcoidosis, a feature in common with other types of mediastinal adenopathy where there is no invasion or direct inflammatory extension because of the fairly rigid anatomical structure of the adult tracheobronchial tree.

Electrocardiograms were done on 17 patients without clinical evidence of unrelated cardiovascular disease. The electrocardiograms were normal in 15, and in 2 patients showed evidence of right ventricular strain secondary to extensive pulmonary changes. This finding is presumptive evidence against the presence of myocardial involvement in any of these patients, although the incidence of myocardial infiltration in autopsied material is about 20 per cent (8). Sarcoid infiltration of the myocardium may be present, however, without electrocardiographic changes unless anatomically located to involve the conduction system or sufficiently extensive to cause definite functional damage.

The high frequency of patients with sarcoidosis who fail to react to the tuberculin test is a well-established fact. The reported incidence of this anergy

varies considerably in different series, in many instances probably owing to failure to carry the tests up to full dilutions employing both OT and PPD. McCort and his co-authors (53), for example, report 21 nonreactors among 25 patients with sarcoidosis. Many of these nonreactors, however, were not carried up to full strengths and might well have shown sensitivity at lower dilutions. In Hauser's series (34), 13 among 17 patients with sarcoidosis were reported as nonreactors, and Longcope (10) found 22 nonreactors among 26 patients with the disease. In both series, however, the dilutions to which these tests were carried are not recorded.

In this series, 51, or 98 per cent, of the patients were tuberculin tested at least once during the course of their disease. Thirty-three, or 65 per cent, are classified as nonreactors. Sixteen of these patients failed to react to 1.0 mg. of OT, 12 did not respond to .005 mg. of PPD, and 5 patients were nonreactors to both 1.0 mg. of OT and .005 mg. of PPD. Four patients failed to react to lesser strengths of either PPD or OT, but are not listed as nonreactors because the tests were not carried to full strengths. The incidence of nonreactors in this series is more comparable to that in Reisner's group (1), in which 60 per cent of the patients failed to react to doses as high as 1.0 mg., and to that in Oppenheim and Pollack's series (33), in which 64 per cent of their patients failed to react in dilutions of 1:100 OT.

Among these 37 patients, 4 were reported as showing positive tuberculin tests at other hospitals or clinics, which were not confirmed during later hospitalizations at Bellevue. Whether there was a loss of previously established tuberculin allergy in these 4 instances, a phenomenon which has been observed in sarcoidosis (37), or whether there was a misinterpretation of a negative skin test is not clear. The difficulties in reading an equivocal tuberculin test in Negroes are well known and the most likely explanation of this discrepancy was the misinterpretation of a negative skin reaction.

It has been claimed that the positive reactors react weakly and then only to large test doses. Although there is no specific information as to the intensity of the reactions in these 14 patients, 3 responded to 0.1 mg. of OT; 3 to 1.0 mg. of OT; 1 to .00025 mg. of PPD; and 6 to .005 mg. of OT. One patient reacted only to 2 mg. of OT.

Miscellaneous studies of allergy included the findings of anticutins in one case. This patient with pulmonary parenchymal disease also failed to show any evidence of a focal reaction to massive doses of tuberculin.

It is quite probable that some of the nonreactors in this series would have shown a positive reaction to lesser dilutions. This high incidence of nonreactors to the usually accepted dosages is undoubtedly higher than in a comparable racial, urbanized, and similar age group with a similar socio-economic background. The interpretation of this anergy has provoked much discussion and will be mentioned elsewhere.

ROENTGENOGRAPHIC FINDINGS

The roentgenographic findings of interest are related to the osseous lesions and changes present in the chest. The osseous lesions show a predilection for

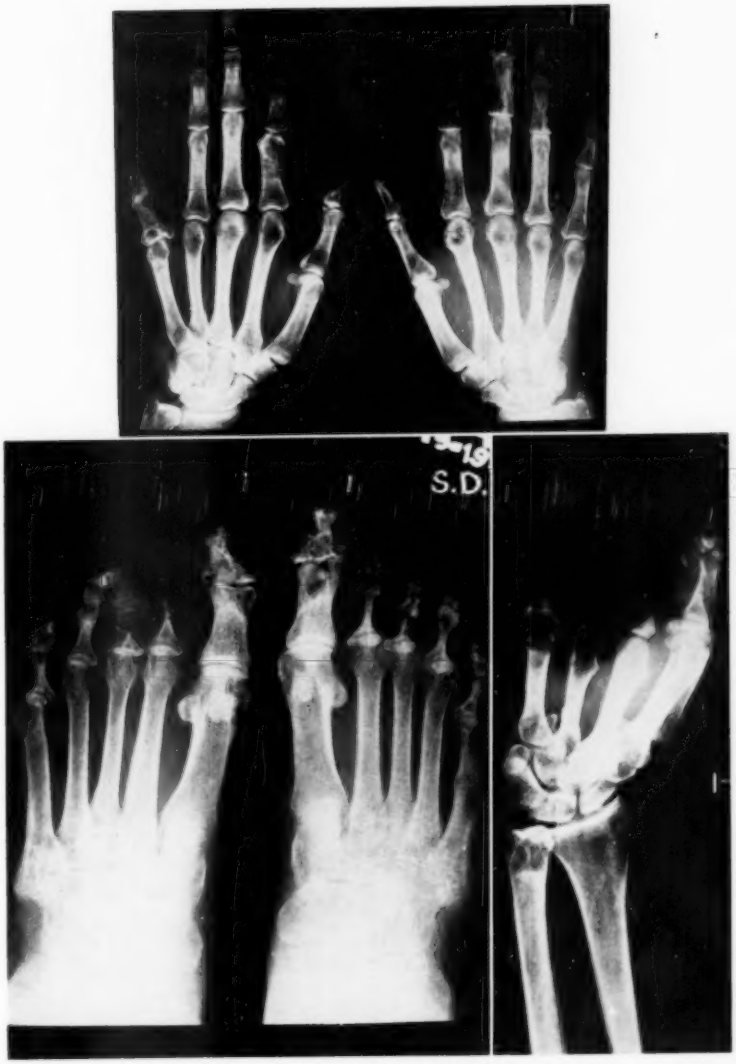

FIG. 1. Patient S. D.

a. (Top) Roentgenograms of the hands showing extensive changes in the phalanges and metacarpal bones consisting of cystic destruction, necrosis, and bone resorption with cortical involvement but with relatively little joint involvement.

b. (Lower left) Roentgenograms of the feet showing changes in the phalanges and metatarsal bones similar to those present in the hands.

c. (Lower right) Cystic changes in the distal end of the ulna.

the phalanges, although lesions have been demonstrated in the long bones and elsewhere. These changes have recently been reviewed by Holt and Owens (54), and consist essentially of two types which were demonstrated with about equal frequency in the 7 patients with roentgenographically demonstrable bone lesions in this series. The first type consists of well-localized punched-out cystic areas without evidence of surrounding inflammatory reaction. The second type, considered more characteristic of sarcoidosis, consists of marked alteration in the trabecular structure of the bone with extensive cortical atrophy and resorption. A coarse reticulated appearance of the medullary portion of the bone is charac-

FIG. 2. Patient F. V. Roentgenograms of the foot showing characteristic coarse trabeculation and "lattice-work" changes in the phalanges and metatarsal bones.

teristic. Pain is conspicuously absent. These lesions, when extensive, are usually accompanied by soft tissue swelling, and may produce mutilating deformities. The changes are thought to represent trophic disturbances secondary to interference with the blood supply by infiltration of the medullary portion of the bone by sarcoid tissue. Periosteal and joint involvement is infrequent, although it may occur in advanced cases (55). There was one case of cystic involvement of a long bone and two instances of nasal bone involvement, both in patients with sarcoid involvement of the bridge of the nose. According to Holt and Owens, this combination is not uncommon. One patient with extensive osseous phalangeal changes showed evidence of pathologic fractures. The relationship between the two types of lesions is not known but is probably related to the severity and extent of involvement. These changes are similar to those seen in

leprosy (56), but other characteristics of leprosy, such as sensory changes, are invariably absent in sarcoidosis.

The roentgenographic appearance of the pulmonary lesions is nonspecific and may resemble several other conditions, among which are lympho-hematogenous tuberculosis, diffuse interstitial fibrosis of unknown etiology, diffuse lymphangitic

FIG. 3. Patient V. C. Solitary cystic lesion present in the proximal end of the middle phalanx of the right middle finger.

carcinomatosis, silicosis, congestive failure, bronchiolitis, and (of more recent cognizance) pulmonary fibrosis secondary to exposure to beryllium. The findings in each individual patient are variable dependent upon the phase of the disease, but there appear to be certain predominating patterns. Since these often coexist, classification is difficult and perhaps artificial. It is believed, however, that recognition of the different roentgenographic patterns may have some prognostic significance.

These patterns have been described in detail by Reisner (1), Bernstein and

Sussman (57), and Bernstein (58), and the findings in this group are quite comparable to those described by these authors. As noted, 7 patients demonstrated only mediastinal adenopathy unaccompanied by evidence of pulmonary parenchymal involvement (figure 4). Fourteen, or 31 per cent, of the patients with pulmonary lesions showed changes of a linear strand-like nature, radiating out in a fan-shaped fashion from both hilar areas and invariably accompanied by massive hilar adenopathy. Nine, or 20 per cent, of the patients showed diffuse changes consisting of widely disseminated bilateral nodular foci evenly distributed throughout both lung fields. These nodules were sometimes larger and coarser than the lesions of true miliary tuberculosis. In this group the

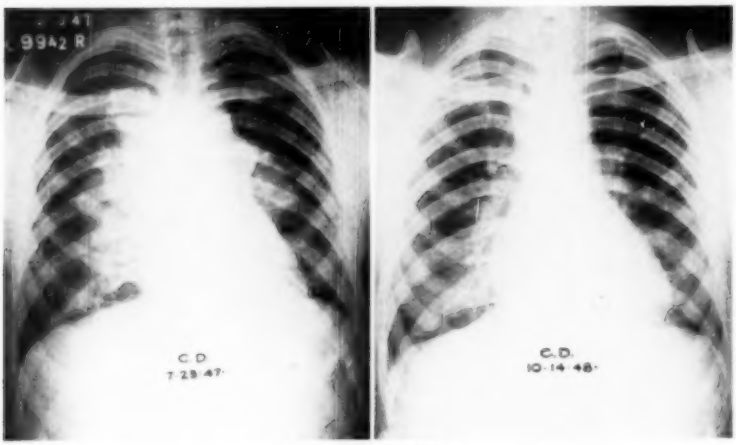

FIG. 4. Patient C. D.

a. (Left) July 23, 1947. Extensive hilar and paratracheal adenopathy without definite evidence of pulmonary involvement.

b. (Right) October 14, 1948. Marked spontaneous clearing of the adenopathy which, presumably by coincidence, followed a diagnostic course of radiation delivered over the right anterior mediastinum.

mediastinal adenopathy did not appear so marked but in several instances was obscured by the overlying pulmonary disease. Reisner found that approximately one-third of his cases fell into each one of these two main groups. Ten patients, or 22 per cent, of the group with pulmonary changes showed a combination of the two types of pattern without a particular predominance.

In 8 cases, or 18 per cent, of this group with parenchymal involvement, the changes consisted of diffusely scattered, more confluent patchy densities than in the cases with discrete nodular densities. In 3 instances the pulmonary infiltration consisted of a soft granular pattern, and one patient showed a pneumonic primarily unilateral consolidation consistent with either a pyogenic or tuberculous pneumonia, without, however, any clinical findings to support either diagnosis.

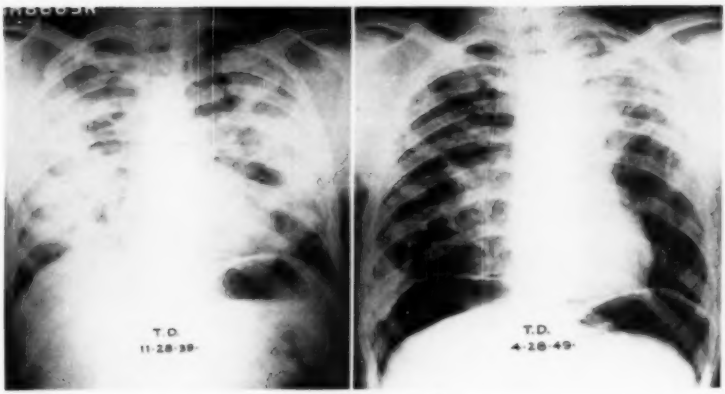

FIG. 5. Patient T. D.

a. (Left) November 28, 1939. Bilateral exudative soft confluent lesions with tenting of the diaphragm.

b. (Right) April 28, 1949. Severe bilateral fibrosis and emphysema with active pulmonary tuberculosis of the left upper lobe treated ineffectually with streptomycin and pneumoperitoneum.

FIG. 6. Patient M. W.

a. (Left) October 13, 1945. Bilateral hilar node involvement with a prominent enlarged right paratracheal node. No parenchymal involvement is present at this time.

b. (Right) May 29, 1947. The adenopathy is still present and there is now bilateral parenchymal infiltration consisting of scattered nodular densities which in some areas appear confluent.

The correlation between the roentgenographic appearance and the morphology of early lesions, especially in those cases showing complete roentgenographic reversibility, is difficult, as autopsy findings are generally confined to those patients who die of either extensive tuberculosis or right heart failure secondary

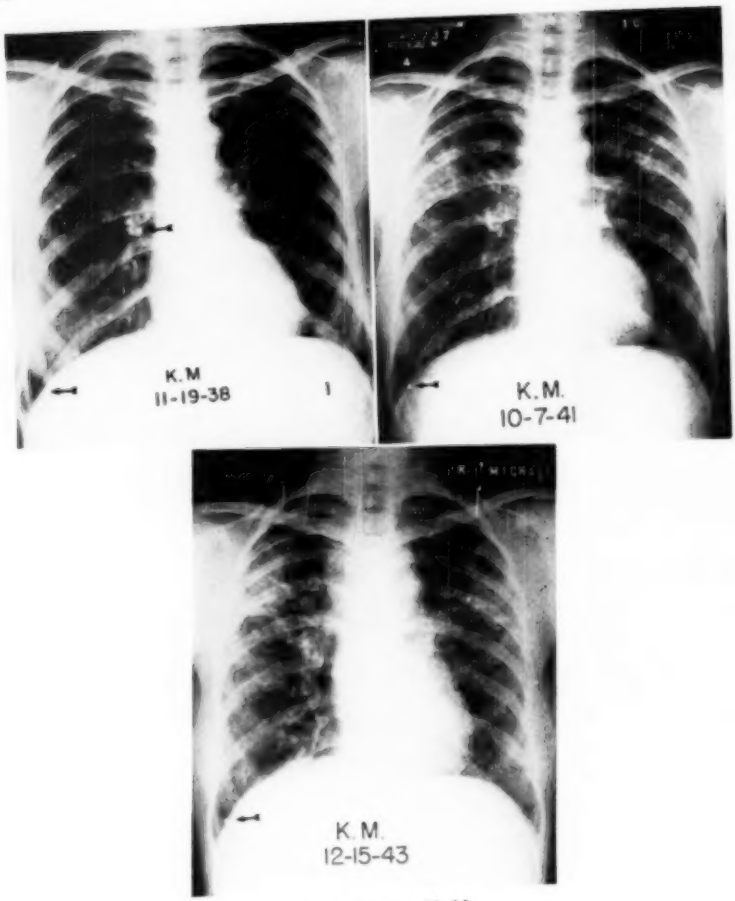

FIG. 7. Patient K. M.

a. (Upper left) November 19, 1938. A negative roentgenogram except for the presence of extensive calcification of the right hilar lymph nodes and two calcific nodules in the right lung.

b. (Upper right) October 7, 1941. Early bilateral fibrotic changes predominantly in the upper halves of both lung fields.

c. (Bottom) December 15, 1943. Further progression of bilateral pulmonary fibrosis with marked enlargement of the right paratracheal node. Despite the extensive hilar calcification with parenchymal calcific foci, this patient failed to react to full strength OT.

to irreversible pulmonary fibrosis. The usual explanation offered for the appearance of these lesions relates it to the disposition of sarcoid tissue along the perivascular and interstitial septal lymphatics. Another explanation given is that the changes are secondary to lymphatic obstruction and stasis, due to either

pressure from enlarged hilar nodes or to actual edema and stasis within the node itself (59). It is postulated that this causes blockage of the draining lymphatic system, resulting occasionally in fibrotic changes. This hypothesis is substantiated by the finding that often the pulmonary lesions develop following the mediastinal adenopathy (figure 6) and regress simultaneously with lymph node regression, but occasionally the converse may be true. The roentgenographic clearing may also be explained by the capacity of the sarcoid tubercle to resolve completely. It is not definitely known, however, whether roentgenographic clearing always indicates complete anatomical reversibility and freedom from pathologic changes not demonstrable roentgenographically.

Although Reisner believes that the two different roentgenographic patterns represent transitional stages in the disease, sufficient evidence from this series is lacking to support his contention. Corroborating evidence is also lacking to substantiate his belief that the nodular type of infiltration represents the early stages of the disease, except in the sense that it may be the precursor of either pulmonary tuberculosis or irreversible pulmonary fibrosis. This pattern has generally presented a full-blown picture at the time of roentgenographic examination of the chest. In one patient, K. M., symmetrical areas of fibrosis were localized to both upper lung fields with the remaining pulmonary parenchyma roentgenographically free from disease. Over a period of a few years the fibrotic changes progressed to involve the entire remaining lung fields (figure 7). This case however, is somewhat atypical.

Nine, or 17 per cent, of the cases showed pleural changes consisting of diaphragmatic tenting, blunted costophrenic angles, and pleural thickening. In the majority of instances these findings probably antedated the onset of sarcoidosis. Nine cases showed the presence of either calcified hilar nodes or a calcified parenchymal nodule with or without calcified hilar nodes, in this geographical area presumptive evidence of a healed tuberculous primary complex. This finding has been reported not infrequently on autopsy findings in cases of sarcoidosis otherwise unassociated with tuberculosis.

Case Report

Case 5. M. B., a 27-year-old white male, was admitted to the Psychiatric Service of Bellevue Hospital on September 21, 1948, because of attempted suicide. In February 1939, a chest film was interpreted as showing pulmonary tuberculosis, and he was admitted to a tuberculosis sanatorium in May 1939.

Physical examination at that time revealed a well-nourished young male. Resonance over the upper halves of both lung fields was impaired, with normal breath sounds and no rales. Large discrete rubbery lymph nodes were palpable in both axilla and inguinal areas and in the right epitrochlear region. The sputum and two gastric aspirates were negative for tubercle bacilli. The tuberculin test, 1.0 mg. of OT, was negative. A roentgenogram taken May 23, 1939, showed an extensive infiltration involving principally the middle third of both lungs with extension towards the apex and base. The densities were most marked at the level of the hilum with peripheral clearing. Both diaphragms were tented and the right costophrenic angle was obliterated. Roentgenograms of the hands and feet were normal.

During his hospitalization the patient was relatively asymptomatic. Biopsy of material from a left axillary node showed dense seeding of epithelioid tubercles without caseation and with very few giant cells. No tubercle bacilli were seen on section.

The patient was discharged on July 2, 1939, with a diagnosis of noncaseating pulmonary tuberculosis and was well when last seen in March 1941.

On March 26, 1948, he was admitted to another hospital with a history of increasing dyspnea, occasional chest wheeze, weight loss, and anorexia for about six months. On physical examination he was cachectic and apprehensive. Scattered wheezes were heard throughout his chest, with occasional sibilant rales and a prolonged respiratory-expiratory phase. No palpable nodes were present. A chest film is reproduced in figure 8.

During hospitalization of this patient, his temperature ranged between 99° and 100°F. The serum proteins were 6.9 gm. per 100 cc. with an A/G ratio of 3.6/3.3. Sputum was negative for tubercle bacilli. Since the patient was expectorating large quantities of foul

FIG. 8. Patient M. B. Extensive pulmonary fibrosis and emphysema resulting from pulmonary sarcoidosis of at least nine years' duration. The fibrocalcific nodule found at autopsy in the left upper lobe is not visualized.

pus, it was believed an underlying suppurative process was present, and he was given a course of aerosol penicillin with good results. Sputum decreased and became odorless, dyspnea and wheezing diminished, and temperature became normal. He was discharged as improved on April 11, 1948.

On May 28, 1948 he was readmitted to the same hospital because of increased dyspnea and wheezing, with cyanosis and edema of the lower extremities. Except for these findings, physical examination was essentially unchanged. The total leukocyte count was 19,800 cells per cu. mm. with 81 per cent polymorphonuclear leukocytes. Temperature was 104°F. A chest roentgenogram was unchanged and an electrocardiogram showed right-axis deviation. Examination of the sputum was again negative for acid-fast bacilli. On aerosol penicillin his condition improved sufficiently so that he was discharged on June 15, 1948.

In July 1948 he was again admitted with an exacerbation of the same symptoms. On

oxygen, expectorants, penicillin, postural drainage, and digitalis he showed improvement, and was transferred to Bellevue on September 21, 1948.

Physical examination on admission revealed a chronically ill, cyanotic and dyspneic white male with dependent ankle edema. The lungs were hyper-resonant throughout with diminished breath sounds and bilateral rales. There was slight increase in the antero-posterior diameter of the chest. Cardiac examination revealed only that the second pulmonic sound was greater than the second aortic sound. His course was progressively downhill and he became increasingly dyspneic and cyanotic in spite of oxygen administration. He died on October 3, 1948.

The pertinent gross and microscopic necropsy findings were as follows: "On reflecting the sternum several enlarged firm lymph nodes were noted. Both pleural cavities were almost completely obliterated by firm, fibrous adhesions. The mediastinal glands were enlarged and firm and on section showed mottled areas of anthracosis with areas having a fleshy appearance. No calcification or caseation was noted. There was also marked enlargement of the preaortic and mesenteric nodes. The heart was enlarged and weighed 320 gm., with marked dilatation and hypertrophy of the right side with a prominent pulmonary conus. The right ventricular wall measured 6 mm. in thickness. The left side of the heart also showed some dilatation. The lungs were covered on their pleural surfaces by shaggy fibrous tags, and scattered over both were numerous raised small, firm, pale grayish-white patches which appeared to be composed of confluent, small tubercle-sized lesions. On section a fibrotic mass was present in the left upper lobe which was hard and deeply pigmented. Scattered elsewhere were numerous grape-like clusters of small whitish tubercle-like lesions. The bronchi were filled with a mucopurulent exudate. The appearance of the right lung was essentially similar. The other organs were grossly normal."

Microscopic Examination

Considerable myocardial hypertrophy of the right ventricle was present, with some increased interstitial fibrosis. Except for the lymph nodes, which showed numerous epithelioid tubercles without caseation with rather sparse giant cells, the remaining pertinent findings were confined to the lungs. A few scattered noncaseating tubercles were in the spleen.

Several sections from the lungs were available:

Slide No. 1: This section showed numerous epithelioid tubercles. They occurred singly and in groups and many were gathered in thick dense bands of partially hyalinized connective tissue. Many showed partial or complete fibrosis and contained many giant cells. There was little or no zone of peripheral lymphocytes and there was no caseation. The uninvolved lung was small in amount, and showed marked emphysematous changes. The alveolar walls were very thin and many were broken.

Slide No. 2: The pleura was thickened by fibrous tissue. The normal alveolar structure was almost completely replaced by fibrous tissue in which were seen numerous tubercles and considerable granulomatous tissue composed of epithelioid cells and giant cells. Much of this fibrous tissue was hyalinized. The alveolar walls were in many cases thickened by fibrous tissue often containing an infiltration of lymphocytes and plasma cells. The remaining lung parenchyma was emphysematous and atelectatic.

Slide No. 3: This section was through a fibrotic area in which the greater part of the fibrous tissue was completely hyalinized, and contained numerous rounded and completely hyalinized tubercles. It contained several large areas in which deposits of calcium were in this hyalinized tissue, and scattered in many other areas were similar, small, often rounded calcific deposits. Some other tissue similar to that described previously was also found.

Slide No. 4: This section again showed marked fibrosis and anthracosis with calcification and epithelioid tubercles and granulation tissue. In addition, in one area there was a bronchus containing cellular debris surrounded by granulomatous hyalinized connective tissue. Along one margin the fibrous tissue appeared necrotic, and the bronchi in this region with involved walls appeared somewhat dilated.

Slide No. 5: In this section similar changes were again noted. In addition, several fairly

large areas of necrotic material showing calcium deposition and cholesterol clefts were present. The bronchial walls had been destroyed and replaced by granulomatous chronic inflammatory tissue.

Slide No. 6: Groups of tubercles were seen in this section. One asteroid body was seen within the cytoplasm of a giant cell in the center of one of the tubercles.

Acid-fast stains were negative as were culture and guinea pig inoculations for tubercle bacilli.

Final Anatomical Diagnosis

Granulomatous lesions of lungs, spleen, and lymph nodes, probably Boeck's sarcoid; fibrocalcific nodule, left upper lobe; fibrous pleural adhesions, bilateral; hypertrophy and dilatation of the right ventricle.

Comments on this case: Dr. Marvin Kushner (pathologist): This patient represents one of those cases with chronic fibrosing granulomatous disease of the lung in which caseation is not a feature and no tubercle bacilli are found. It is of interest that the patient's tu-

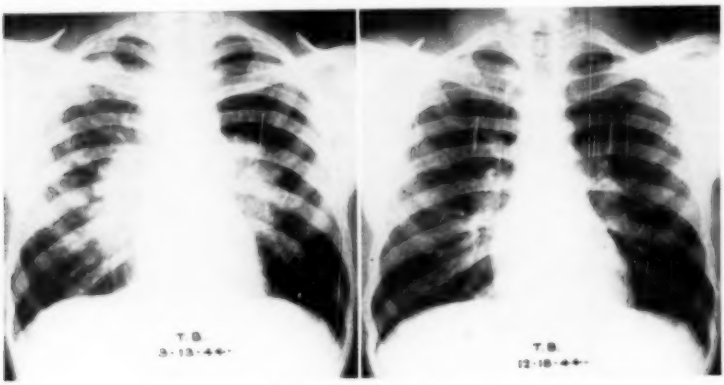

FIG. 9. Patient T. B.

a. (Left) March 13, 1944. Extensive bilateral mediastinal adenopathy with linear streaking shadows radiating out into both lung fields. A good example of the so-called "potato nodes."

b. (Right) December 18, 1944. Marked spontaneous clearing occurring within several months.

berculin skin test was negative. From the previous lymph node biopsy and from the lesions demonstrated at autopsy, this patient would appear to fall into the group of Boeck's sarcoid. The unusual feature here is the presence of a fibrocalcific scar of the left lung which is suggestive of healed primary tuberculosis. In one section, too, there is an area of calcification and cholesterol clefts, now encapsulated, which may represent old fibrocaseous disease. The moderate degree of cor pulmonale is characteristic of the interstitial fibrosis with compensating emphysema and perivascular and peribronchial fibrosis seen in this case.

Although certain authors (6) believe that there is no connection between the type and distribution of the pulmonary lesions in relation to prognosis, some slight correlation does appear. Almost 40 per cent of the patients who showed roentgenographic clearing of the pulmonary lesions demonstrated the linear fan-like infiltration extending out from both hila and accompanied by large nodes (figure 9). The patients with widely disseminated nodular foci, especially

those showing a tendency to coalesce, seemed during the period of observation more prone to develop progressive changes, fibrosis, or pulmonary tuberculosis. This differs from Reisner's observations that the nodular disseminated infiltrations showed the most marked tendency to clear. The discrepancy is difficult to explain. The lesions which remained stationary showed no particular predominating pattern. The shortest period of complete regression occurred within a few months, although the disease may already have been in a regressive phase when first demonstrated by roentgenographic examination. In most instances, clearing occurred over a period of several years. The patients who developed tuberculosis in some instances showed cavitation superimposed on pre-existing disease or else increased confluency and evidence of pneumonic changes. In those with progressive fibrosis there was a slow resolution of any exudative elements, with the development of a stringy, scattered, sometimes reticulated, fibrosis. In several cases emphysematous blebs were present, most probably secondary to a chronic organizing constrictive bronchiolitis and peribronchiolitis or to granulomatous invasion by sarcoid tissue, with irreversible damage to the muscular and elastic tissue. These blebs have frequently been demonstrated in autopsy material.

COURSE AND SEQUELAE

Boeck's sarcoid tends to run a chronic, prolonged course extending over a period of years before the ultimate outcome is reached. In most instances the symptomatology develops in a gradual and insidious fashion. The course of individual lesions appears to be independent of the course of lesions elsewhere in the same individual. Ocular lesions may progress in association with pulmonary clearing or skin lesions may regress or remain stationary simultaneously with progression of the pulmonary disease. Adenopathy, hepatomegaly, and splenomegaly may all be transient phenomena which appear or subside, sometimes to recur, at any stage of the disease.

The literature contains repeated references to the benign course and favorable prognosis of this disease. It is believed that this has been greatly overemphasized and possibly arises from a failure to follow cases over a length of time sufficient to determine the actual outcome. From the findings in this series, in which the majority of patients have been followed for an average of almost five years, we agree with Reisner that "one is not justified in assuming too confident an attitude regarding the ultimate outcome," and also with Zimmerman and Mann (61) that the prognosis of the disease should not be considered with the optimism that has prevailed up to the present.

Directly related complications included episodes of recurrent spontaneous pneumothoraces in 2 patients. It is believed that this complication is not coincidental, but, as suggested by Isbister (62), is directly related to the pulmonary pathology and is secondary to the rupture of emphysematous blebs or, as a less likely possibility, secondary to necrosis of a subpleural tubercle.

Cor pulmonale resulting from encroachment upon the pulmonary vascular bed by the granulomatous process was present in 4, or 8 per cent, of the 52 cases. In 3 of these patients the clinical diagnosis was confirmed on autopsy

examination. The entire group of patients in this series were singularly free from repeated lower respiratory tract infections, in spite of extensive pulmonary changes. Only one case (M. B.) already mentioned was complicated by the development of recurrent episodes of suppurative pneumonia.

Among the most serious complications are those secondary to ocular involvement, and these appear to be related to the severity of involvement. Posterior synechiae, corneal opacities, and phthisis bulbi have been frequently observed. In this series, 5, or 47 per cent, of the 12 patients with uveal tract changes developed irreversible disabling damage seriously compromising their vision. Three patients, or 25 per cent, of this group of 12 cases developed secondary glaucoma. Several developed phthisis bulbi. In only one instance was there complete regression of the ocular lesions without sequelae. This high incidence of serious ocular complications is not unique. Kaplan (63), in reviewing reports of

TABLE 7

Summary of Follow-up

	NUMBER	PER CENT
Known deaths related to sarcoidosis	10	19
Living; active tuberculosis	7	13
Progressive pulmonary changes or irreversible fibrosis	5	10
Disease stationary	5	10
Disease regressing	10	19
Complete resolution of disease	7	14
Deaths unrelated to sarcoidosis	3	6
Living; status not known	1	2
Followed too short a time for evaluation	4	8
Total	52	100

43 patients with ocular sarcoidosis, found that 10 developed phthisis bulbi which was bilateral in 7 instances, and that 7 per cent of the patients developed complete blindness. These complications were presumably the sequelae of uveal involvement. Kerley (47) believes that the most serious clinical manifestation of sarcoidosis is the development of an iridocyclitis.

The over-all outcome in this group of patients is presented in table 7. Among these patients, 4 were followed for too short a time for evaluation of the course of their disease, one patient was living but his clinical status was not known, and 3 patients had died from unrelated causes.

The percentage of patients in comparable series with complete regression of the disease shows considerable variation. Reisner found among his patients, with an average follow-up of approximately five years, that complete regression occurred in about one-third.

King (64), in a series of 37 patients with sarcoidosis, found that there was complete clearing in 23 instances and progression in only 3. In this series, only 7 patients, or 13 per cent, of the entire group showed complete resolution

with no symptoms and no clinical or roentgenographic evidence of the disease. This incidence of complete clearing undoubtedly would be higher with longer follow-up on 10 additional patients who showed signs that their disease was regressing. Many of these patients had extensive pulmonary lesions. It is also true that this regression during the period under observation might have been only a temporary phase with later progression, so judgment as to the final outcome in this group should be deferred. It has been noted (57), however, that, if the pulmonary lesions disappear, recurrence in the lungs is rare, although the appearance of new pulmonary lesions in the face of a subsiding mediastinal adenopathy is not infrequent. Garland (32) has also found a higher incidence of clearing. The discrepancy is probably best explained by the longer follow-up in this series.

In 5 cases, or 10 per cent, of the group, the disease appeared stationary, with no tendency to either progress or regress over considerable periods of time. In another 5 patients, gradual progression of the disease took place, manifested by either extension of the lesions or the development of irreversible pulmonary fibrosis. It is conceivable that, prior to the development of irreversible damage, some of these manifestations might have eventually subsided if these patients had been observed over a longer period of time. Similar to the outcome in those patients with regressing lesions, the ultimate outcome in this group cannot be predicted with certainty.

The development of clinically active tuberculosis has long been recognized as one of the more common complications of this disease. The reported incidence of this occurrence in different series, however, varies to an astonishing degree. In Garland's series (32), for example, the development of overt tuberculosis was not observed in a single patient. According to Freiman (8), the development of clinically active tuberculosis occurs in about 10 per cent of all reported cases. The incidence in autopsy material (10, 11) is considerably higher, and in all series is probably in direct proportion to the length of follow-up.

In this series of patients, 13, or 25 per cent, of the group developed clinically active tuberculosis. In addition, a fourteenth patient is reported as having died with far advanced tuberculosis, although this diagnosis was not confirmed either bacteriologically or morphologically. These cases are presented in table 8 and deserve some discussion.

The onset of tuberculosis was generally heralded by gradually increasing systemic and respiratory symptoms or by the development of extrapulmonary manifestations. Although this group is small, there appeared to be a slightly higher ratio of females to males than in the entire series and, although Negroes formed 79 per cent of the whole group, 92 per cent of the patients who developed tuberculosis were Negro. With a single exception, all of these patients developed pulmonary tuberculosis, with sputum positive for acid-fast bacilli. The exception was a patient in whom the earlier pulmonary sarcoid lesions had shown complete regression, who had pleural effusion, presumably tuberculous, which developed following the conversion of a negative tuberculin test to a positive reaction. In no instance did pulmonary tuberculosis develop without

TABLE 8

Development of Active Tuberculosis

13 Cases (25 per cent)

PATIENT	SEX	RACE	DURATION OF SARCOIDOSIS	DURATION OF TUBERCULOSIS	LAST KNOWN STATUS	PULMONARY TUBERCULOSIS	EXTRAPULOMNARY TUBERCULOSIS
V. B.	F	N	18 years, 7 months	5 months	Died, 1940	Far advanced	?
J. B.	F	N	3 years, 2 months	10 months	Died, 1939	Far advanced	?
D. B.	F	N	1 year, 6 months	2 years	Hospitalized, August 1949	Far advanced	Osteomyelitis right middle metatarsal
P. C.	F	N	3 years, 3 months	3 months	Hospitalized, August 1949	Far advanced	None
E. C.	F	N	2 months	10 months	Hospitalized, July 1949	Far advanced	? Skin
T. D.	M	N	10 years, 6 months	6 months	Signed out without leave, May 1949	Far advanced	None
A. D.	F	N	2 years, 4 months	2 months	Died, October 1946	Far advanced	None
B. F.	F	N	4 years, 3 months	9 months	Well and convalescent	None	Pleural effusion
O. G.	F	N	2 years	6 months	Hospitalized, August 1949	Far advanced	Cervical node
D. M.	M	W	3 years	3 years	Died, July 1948	Far advanced	Liver, kidney, spleen
B. S.	F	N	1 year, 7 months	5 months	Died, November 1947	Far advanced	? Liver and spleen
L. W.	M	N	1 year, 4 months	2 months	Died, October 1942	Far advanced	Lymph nodes, myocardium, liver, spleen, skin, adrenals, kidneys
A. W.	F	N	5 months	3 months	Hospitalized, August 1949	Far advanced	Chest wall abscess

pre-existing sarcoidal involvement of the lungs. The duration of sarcoidosis preceding the development of tuberculosis was variable, ranging from more than eighteen years to a few months. Usually, however, the duration of sarcoidosis was between two and three years. Following the development of tuberculosis,

these patients did poorly and ran a chronic slowly downhill course. Six patients died from progressive tuberculosis; the others, excluding the patient with the pleural effusion, who was well and convalescent without any other definite manifestations of extrapulmonary tuberculosis, required prolonged periods of hospitalization for indefinite periods of time. Although the course of the disease was generally chronic and protracted, in some patients it was rapidly progressive

TABLE 9

Summary of Known Fatal Cases

13 Cases (25 Per cent)

PATIENT	SEX	RACE	AGE AT DEATH	AUTOPSY	DURATION OF ILLNESS	CAUSES OF DEATH
V. B.	F	N	36	No	19 years	Pulmonary tuberculosis
J. B.	F	N	22	No	4 years	Pulmonary tuberculosis
M. B.	M	W	37	Yes	9 years	Pulmonary sarcoidosis with cor pulmonale, respiratory insufficiency, and right heart failure.
V. C.	F	N	43	Yes	4 months	R.H.D., congestive failure, uremic pericarditis, rheumatic myocarditis (sarcoid an incidental finding).
A. D.	F	N	46	Yes	2½ years	Pulmonary tuberculosis, pulmonary sarcoidosis, cor pulmonale, and right heart failure.
C. J.	F	N	40	No	8 years	Spontaneous pneumothorax
B. K.	M	W	30	Yes	6 years	Uremia, congenital fused left polycystic kidney, nephrolithiasis, chronic pyelonephritis, uremic pericarditis, acute interstitial right ventricular myocarditis.
D. M.	M	W	35	Yes	6 years	Pulmonary tuberculosis wth hematogenous dissemination to liver, kidneys, and spleen.
J. R.	M	N	29	Yes	8 months	Cor pulmonale and right heart failure with respiratory insufficiency secondary to pulmonary sarcoidosis.
B. S.	F	N	25	No	2½ years	Pulmonary tuberculosis
F. S.	F	N	26	No	1½ years	? pulmonary tuberculosis
I. W.	M	N	45	Yes	6 years	S.B.E. of tricuspid valve, myocardial fibrosis, cardiac dilatation and failure.
L. W.	M	N	35	Yes	1½ years	Tuberculosis of lymph nodes, myocardium, lungs, liver, spleen, adrenals, skin, kidneys.

and fatal within a few months. Several patients, in addition to pulmonary tuberculosis, demonstrated either clinical evidence of extrapulmonary hematogenous tuberculosis or were found at autopsy to have widely disseminated foci of the disease.

As already noted, there were 13 deaths. Ten, or 19 per cent of these were directly related to sarcoidosis, including those patients who died from far advanced tuberculosis. These deaths are summarized in table 9. Among these

patients were the 2 already mentioned as having been reported previously. The first of these, B. K., was erroneously reported in 1942 by Rottenberg and Guggenheim (2) as a presumptive case of renal sarcoidosis and was later referred to by Klinefelter and Salley (3) in a discussion of this condition. This patient is also mentioned by Rubin in his textbook on chest diseases (4). The clinical and pathologic findings in the second previously reported case, I. W., are discussed by Rosenthal and Feiger (5).

It will be noted that there is an almost equal distribution between males and females and that the incidence of deaths related to sarcoidosis among Negroes was 80 per cent as compared with an incidence of 79 per cent in the entire series of cases. This is of interest when compared with the higher frequency of complicating tuberculosis among Negroes. The duration of illness prior to fatal termination was usually long and protracted. In one case (J. R.), however, only six months elapsed between the onset of symptoms and the development of severe pulmonary insufficiency and eventual right-sided cardiac failure. Advanced tuberculosis accounted for the majority of deaths. Others resulted from cor pulmonale and right-sided heart failure. One patient died with a spontaneous pneumothorax at another hospital.

The incidence of organ involvement found at autopsy in general paralleled clinical involvement. Among the 5 autopsied cases uncomplicated by tuberculosis, lymph node involvement was present in 5, pulmonary involvement in 4, splenic and liver involvement in 3, testicular involvement in 2, skin involvement in one, and renal involvement in another.

The following case reports are presented to illustrate particular points of interest already mentioned. One of these (B. L.) died following the completion of this study, so was not included among the original 52 cases.

Case Reports

Case 19. A. D., a 42-year-old Negro female, was first admitted to Bellevue Hospital on November 15, 1945 with the complaints of easy fatigue for about eighteen months, moderate dyspnea for several months, cough productive of about one-half cupful of mucopurulent sputum of about two weeks' duration, fever, and weight loss. Physical examination revealed a febrile Negro female in no distress. Palpable nontender discrete nodes were present in the right axilla and in both inguinal regions. Many medium, moist, posttussic rales were present throughout both lung fields, with scattered wheezes and rhonchi and bronchial breath sounds over the right posterior apex. The second pulmonic sound was greater than the second aortic sound. The spleen was palpable and the liver percussed below the costal margin.

Many sputum smears and one sputum culture were negative for tubercle bacilli. No fungi were present. The serum proteins were 10.3 gm. per 100 cc. with an A/G ratio of 3.6/6.7. The erythrocyte sedimentation rate was 107 mm. per hour; alkaline phosphatase, 17; tuberculin test was negative to .005 mg. of PPD. The electrocardiogram was normal. An abdominal flat plate showed splenic enlargement to the iliac crest. Roentgenograms of the hands and feet were negative. A chest roentgenogram showed a diffuse nodular infiltration. The right costophrenic angle was obliterated.

On bed rest the temperature ranged between 99° and 100° F., and sputum became scant. The patient was discharged on December 14, 1945 with the diagnosis of sarcoidosis.

She was readmitted to Bellevue on August 14, 1946 because of increasing dyspnea, fatigue, cough, and sputum. She was emaciated, slightly cyanotic, and very dyspneic. Many rales

were present throughout the left lung, with bronchial breath sounds at the apex and coarse rales with amphoric breath sounds on the right with patchy areas of dullness. The liver edge was firm and just palpable; the spleen could no longer be felt.

Sputum was positive on direct smear for acid-fast bacilli. A tuberculin test was positive to .001 mg. of OT. Chest roentgenograms showed a mixed soft and fibrous-appearing infiltrate with confluency on the left and a large cavity on the right. Her course was progressively downhill, roentgenograms showed progression, and the patient died on October 18, 1946.

The pertinent gross autopsy findings were as follows: There were dense apical and lateral pleural adhesions on both sides. The anterior mediastinal nodes were not enlarged. There was dilatation and hypertrophy of the right ventricle, the wall of which measured 4 to 5 mm. in thickness. The pulmonary conus was somewhat dilated and the pulmonary valve measured 8 cm. in circumference. The lungs were nodular in appearance with many superficial tubercles. The bronchial lymph nodes were enlarged, and on section some were caseous and calcified; others, fleshy and black. Both lungs were riddled with tubercles, with the right upper lobe almost completely replaced by a huge cavity traversed by numerous small vessels. Many other small cavities were present throughout as well as evidence of marked congestion. The liver appeared slightly enlarged and weighed 1,200 gm. with a coarsely nodular-appearing surface. The spleen was small, weighing 60 gm., with a lobulated and scarred capsule. A few enlarged mesenteric nodes were found which on section were firm and fleshy. There was a generalized enlargement of the cervical, esophageal, tracheal, hilar, retroperitoneal, aortic, renal, and lumbar nodes, all of which were firm and discrete. The hilar nodes, by far the largest, measured several centimeters in length. Some of these were calcified and caseous.

Microscopic examination: On microscopic examination of the lungs, circumscribed areas of fibrosis consisting of large collections of dense collagenous fibers were scattered throughout. These fibers were often surrounded by an area infiltrated by lymphocytes, plasma cells, and other round cells. This fibrous capsule surrounded the blood vessels and bronchial branches in some places. Scattered in the lung parenchyma were collections of epithelioid cells with infiltrations of lymphocytes, occasional plasma cells, and atypical giant cells, but with no caseation necrosis. In other areas the alveoli were involved by an interstitial reaction consisting of round cells, and the alveoli contained collections of round cells and polymorphonuclears. These areas and also many of the bronchi containing pus were found to contain acid-fast bacilli. Other sections of the lung, again in close relation to fibrosis, consisted of caseation necrosis surrounded by epithelioid cells and lymphocytes with intervening areas of pneumonitis. This caseation seemed to be of recent origin since alveolar structures could sometimes be made out in many places. Acid-fast stain revealed acid-fast bacilli in areas of caseation necrosis. The liver showed large amounts of hyaline connective tissue replacing much of the portal areas. In the parenchyma were several early tubercles consisting of a granulomatous reaction with Langhans' cells. Similar changes in the spleen showed tubercles of the noncaseating type. Acid-fast stain on one section was negative. The lymph nodes showed varying amounts of swollen hyalin connective tissue. Bordering on these areas in some of these nodes were early tubercles but with no caseation.

Anatomical diagnosis: Fibrocaseous tuberculosis of lungs with cavitation; sarcoid of lungs, spleen, liver, and lymph nodes; right ventricular hypertrophy and dilatation; pleural adhesions; clubbing.

This case is one of those in which both caseating and noncaseating lesions are found side by side. The development of right-sided cardiac hypertrophy is unusual in uncomplicated tuberculosis and is thought to be related to the preexisting pulmonary sarcoidosis.

Case 28. O. G., a 21-year-old Negro female, was first admitted to Bellevue Hospital on April 10, 1947 with the chief complaint of moderately severe right anterior chest pain of a

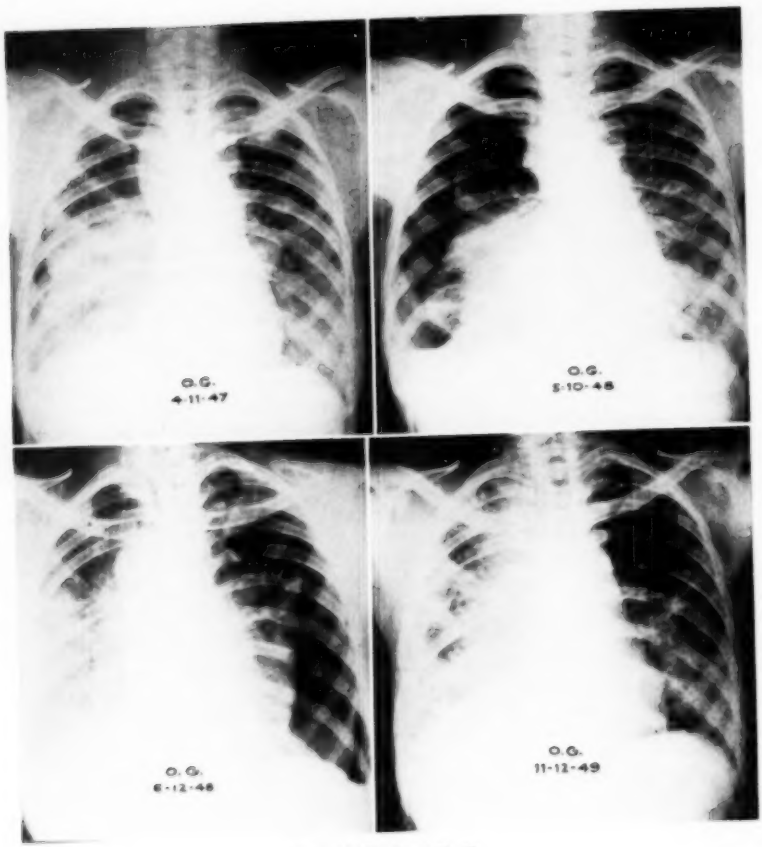

FIG. 10. Patient O. G.

a. (Upper left) April 11, 1947. Bilateral soft exudative-appearing parenchymal infiltration with massive right paratracheal adenopathy. A small right spontaneous pneumothorax is present.

b. (Upper right) May 10, 1948. A second spontaneous pneumothorax with an easily demonstrable bleb of the right middle lobe with a fluid level.

c. (Lower left) June 12, 1948. A third spontaneous pneumothorax of the left lung following a right middle lobectomy with easily demonstrable blebs of the left upper lobe.

d. (Lower right) November 12, 1949. Roentgenogram following the development of clinically active far advanced pulmonary tuberculosis.

few hours' duration, cough productive of less than a cup of sputum daily which was occasionally blood-streaked, and some weight loss. For several months she had noted difficulty with her eyesight.

Physical examination revealed a well-nourished young Negro woman in no distress. Both corneas were cloudy with a surrounding fine punctate nodular deposition. A bilateral

conjunctivitis was also present. Both parotids were palpable. No peripheral adenopathy was noted, and the liver and spleen were not enlarged. The second pulmonic sound was greater than the second aortic sound. Examination of the lungs was negative. An initial chest film is reproduced (figure 10a). Laboratory studies showed an elevated sedimentation rate and were otherwise noncontributory. An electrocardiogram was normal, as were roentgenograms of her hands and feet.

The patient's course was afebrile. On April 30, 1947 preauricular and submandibular nodes became palpable, material from one of which was biopsied on May 30, 1947.

The report of the pathologist is as follows: "Section shows complete destruction of normal lymphoid tissue with replacement by groups of epithelioid cells accompanied by proliferating fibroblasts, lymphocytes, and giant cells. No discrete areas of caseation necrosis may be seen. There is a moderate degree of capillary dilatation and proliferation. Acid-fast stains show no acid-fast bacilli." Culture of the excised node and guinea pig inoculation were negative for acid-fast bacilli.

The iridocyclitis improved only slightly with atropine. Serial films showed gradual resorption of the pneumothorax with no significant change in the infiltration. On May 9, 1947 it was noted that the patient had developed palpable, firm, nontender supraclavicular nodes. She signed out of the hospital on July 7, 1947.

The patient was then followed at intervals in the Chest Clinic. She complained of intermittent episodes of abdominal pain, but gained weight and had essentially no chest symptoms. On September 4, 1947 her spleen was palpable; chest was clear on physical examination. On October 2, 1947 the tuberculin skin test was negative to 0.1 mg. of OT. On April 5, 1948 she complained of shortness of breath of two days' duration. Fluoroscopy and roentgenogram (figure 10b) showed a right hydropneumothorax, and she was readmitted to the hospital on April 5, 1948.

Physical examination, except for the findings consistent with a right pneumothorax, was essentially unchanged. Thoracentesis yielded 150 cc. of straw-colored fluid with a specific gravity of 1.022 and a cell count of 14,000 per cu. mm. This fluid was negative on smear and culture for acid-fast bacilli.

Bronchoscopy on May 14, 1948 revealed narrowing throughout the right bronchial tree. Anteriorly below the upper lobe orifice the main bronchus showed small, reddened, apparently excavated punctate areas. Below this point the bronchus was markedly narrowed and the mucosa appeared to show some granulation tissue. No biopsy was done. Impression was granulomatous lesion of the bronchial tree; etiology, undetermined.

Laboratory studies were essentially the same as on her previous admission. Tuberculin tests with first and second strength PPD were negative. Sputum was negative on smear and culture for tubercle bacilli. Skin tests with OT were also negative up to 1.0 mg. She showed a mild leukopenia with a 14 per cent eosinophilia. Serial films showed little tendency for the lung to re-expand and repeated intrapleural pressure determinations indicated a patent bronchopleural fistula. On May 20, 1948 an exploratory thoracotomy was performed. When the chest was opened, several bullae were seen over the right middle lobe which contained many large and soft small nodules. A large mediastinal mass was noted at the right apex. A biopsy was attempted but, because of vascularity, solidarity, and the presence of transmitted pulsation, was deferred. The lower lobe was shrunken and solid. A small fistula was noted in one of the blebs in the middle lobe. The visceral pleura was thick and edematous. There were numerous miliary excrescences over the mediastinal pleura which had the appearance of metastatic seedings with many enlarged vascular nodes at the hilum. A right middle lobectomy was done.

The report of the pathologist on the removed lobe is as follows: "The central portion of the lobe is thick, firm, nodular, and appears consolidated. The lateral half contains a large, empty, thin-walled multiloculated bleb. On section the nodules are raised above the surface, compact, dry, gray, and the cut surfaces have a translucent granular appearance. The largest one measures 4 by 4 by 1.5 cm. The rest of the lobe is firm, gray, and granular. On section, the pulmonary architecture has been replaced by focal areas of fibrosis which

contain epithelioid cells and in some areas numerous multinucleated giant cells resembling Langhans' cells. Also present are lymphocytes, plasma cells, occasional polymorphonuclears, and large mononuclear phagocytes. No areas of caseation are noted. There is also some peribronchiolar fibrosis with slight dilatation. Many of the alveoli are congested with red blood cells. No tubercle bacilli are seen on acid-fast stain." A guinea pig inoculated with lung tissue showed no evidence of tuberculosis after three months.

At this time streptomycin was given for one week and convalescence was uneventful. Postoperative films showed no change in the parenchymal infiltration. On June 12, 1948 she again became short of breath, and a film showed a left pneumothorax with some mediastinal shift to the right. An intracostal thoracotomy tube was inserted and suction instituted. The lung promptly re-expanded. Since that episode she felt well and signed out against advice on July 9, 1948.

The patient was again followed in the Chest Clinic. By February 14, 1949 the uveitis had recurred and her spleen was easily felt. On March 29, 1949 she was readmitted for the third time with the complaints of fever, increased cough and sputum, chest pain, wheeze, and anorexia of approximately one week's duration. Physical examination showed many scattered wheezes and rales in her lungs. A right uveitis with corneal clouding was present. There was no peripheral adenopathy except for a single, firm, nontender, right supraclavicular node. Liver and spleen were both enlarged and there was moderate curving of her nails. A tuberculin test with first strength PPD was positive two plus. Sputum was easily positive for tubercle bacilli. Because of her high fever and extremely toxic state she was started on a course of streptomycin, 1 gm. daily for forty-two days, with some clinical improvement. On June 6, 1949 the supraclavicular node was biopsied and the report of the pathologist was as follows: "The structure of the node has been completely replaced by a granulomatous lesion and by areas of caseation. The fibrous capsule of the node is infiltrated with numerous lymphocytes and plasma cells. The remainder of the node consists of a very cellular fibrous stroma in which the main cell types are epithelioid cells, plasma cells, occasional giant cells, and some lymphocytes. There are several areas of what appears to be caseation necrosis. Many still retain fragments of lymphocytes and polymorphonuclear leukocytes. Ziehl-Neelsen stain does not reveal acid-fast bacteria."

Case 32. C. J., a 32-year-old Negro female, was first admitted to Bellevue Hospital on January 6, 1940 with complaints of progressive weight loss, anorexia, cough with occasional scanty sputum, and three-flight dyspnea. For two weeks she had had occasional fever and night sweats.

Physical examination revealed a well-nourished, slightly febrile Negro female who did not appear ill. Rales were heard in both lungs, with diminished breath sounds and dullness on the right. Cardiac examination was negative. Palpable lymph nodes were found in both inguinal areas. The liver and spleen were not enlarged.

An initial roentgenogram is reproduced (figure 11a). The erythrocyte sedimentation rate was 40 mm. per half hour. Three concentrated sputum specimens were negative on direct smear for acid-fast bacilli. A tuberculin skin test with .0025 mg. of PPD was positive. Roentgenograms of extremities were normal.

The patient's course in the hospital was uneventful. She was slightly febrile. On January 17, 1940 minimal thickening of the lacrimal glands was noted. Sputum culture for fungi was negative. On January 26, 1940 the rales in her chest were fewer than on admission. She became essentially asymptomatic with no sputum, and on February 16, 1940 was transferred to another hospital for bed rest.

She remained on bed rest for approximately seventeen months. All sputum examinations and a guinea pig inoculation test were negative for acid-fast bacilli. She was discharged in 1941 with the diagnosis of Boeck's sarcoid, and was readmitted to Bellevue Hospital on July 14, 1944 for a lymph node biopsy. During the interim she had been essentially asymptomatic except for occasional cough. Many sputum examinations were negative on smear and culture for tubercle bacilli.

On physical examination she appeared well. Lungs were clear except for diminished breath sounds and tactile fremitus at the left base. Palpable bilateral axillary nodes and a palpable right supraclavicular node were present. Roentgenograms of the hands were negative and a chest film taken on admission showed diffuse, bilateral generalized interstitial fibrosis. On July 15, 1944 material from an axillary node was biopsied and the report of the pathologist was as follows: "The lymph node shows a moderate degree of hyperplasia most marked in the lymphoid pedicles. There is also hyperplasia of the reticulum cells. There are three minute areas composed of epithelioid cells and multinucleated giant cells. Acid-fast stain fails to demonstrate any acid-fast organisms. Additional sections show similar changes."

From January 14, 1948 to January 29, 1948 she was hospitalized at another hospital for a right spontaneous pneumothorax. At this time the essential physical findings were those

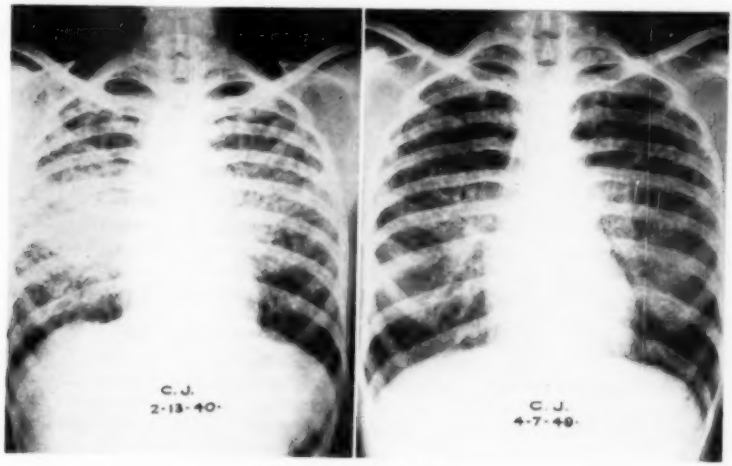

FIG. 11. Patient C. J.

a. (Left) February 13, 1940. Scattered bilateral nodular densities with confluent changes most prominent in the right mid-lung field.

b. (Right) April 7, 1948. Roentgenogram showing diffuse granular and reticulated bilateral pulmonary fibrosis. Shortly after this roentgenogram was taken, the patient had fatal right spontaneous pneumothorax.

of a right pneumothorax, rales at the bases of both lungs, and a firm, palpable left axillary node. The roentgenograms taken on this admission (January 23, 1948) are not available but are described as follows: "The chest shows a fine granular appearance throughout both lungs characteristic of miliary disease. There is evidence of a small degree of pneumothorax on the right." Sputum was negative for tubercle bacilli. She was afebrile. The lung re-expanded uneventfully. The patient was again seen on April 7, 1948, at which time she had no complaints. A roentgenogram of the chest taken at this time is reproduced (figure 11b). She was readmitted on August 9, 1948 with another spontaneous pneumothorax on the right side with a 50 per cent collapse. There was no significant lymphadenopathy at this time and it was noted that the left lung appeared very emphysematous. The patient was found dead in bed in the evening of the day of admission.

As with the preceding case, the course of the disease was complicated by re-

current spontaneous pneumothoraces. The ultimate outcome, however, was development of pulmonary fibrosis and emphysema rather than tuberculosis. The gradual changes on roentgenographic examination of the lungs over an eight-year period are of extreme interest.

Case 53. B. L., a 47-year-old Negro male, was admitted to Bellevue Hospital on August 19, 1949 with the complaints of increasing shortness of breath, cough, and expectoration of about two years' duration.

A roentgenogram taken on May 10, 1935 is described as normal. In 1936 he was hospitalized for pneumonia. The record of this hospitalization is not available.

The patient was well until about May 1946, when he noted the gradual onset of the pulmonary symptoms mentioned. He had no other symptoms until July 1946, when he experienced a sudden episode of acute lancinating pain in the left orbit, followed during the next few months by bouts of photophobia, redness, and gradual diminution of vision. On March 26, 1947 he was admitted to another hospital.

The pertinent physical findings on admission, except for presence of a palpable right cervical node, were confined to the eyes. The conjunctivae were injected and each cornea was hazy. The pupils were irregular, with loss of pupillary reflexes; bilateral posterior synechiae were present and neither fundus could be visualized. Blood pressure was 124 systolic and 86 diastolic. The patient was treated with injections of typhoid vaccine and in addition received streptomycin, without improvement. He was discharged on April 16, 1947. He was readmitted two weeks later, at which time the findings were essentially similar. His vision continued to deteriorate. He received radiotherapy and milk injections without benefit, and was dischargd on May 27, 1947, only to be readmitted on December 11, 1947, at which time the diagnosis of secondary glaucoma of the left eye was made, and a complete iridectomy was performed. His blood pressure at this time was 160 systolic and 110 diastolic. The operation was without benefit.

In January 1948 the patient was seen at a New York City Department of Health chest clinic complaining of cough, sputum, and dyspnea. Chest examination was within normal limits. A tuberculin skin test, strength unknown, was negative. Many sputum examinations were negative for tubercle bacilli. He continued to complain of increasing loss of vision and was put on a regimen of biweekly tuberculin injections without benefit. In July 1948 he was given a course of aureomycin and aureomycin eye drops, without change. On August 9, 1948 he was admitted to another hospital, at which time dependent edema was present. The patient's blood pressure was 178 systolic and 110 diastolic. Crackling rales were heard at the left base posteriorly and laterally. Lenticular opacities and corneal scarring were present. By October 1948 there was complete loss of vision.

Several months prior to admission to Bellevue he had noted the development of multiple flat and raised painless, scaling lesions involving the back, lower extremities, neck, forehead, and bridge of the nose. These lesions were slowly progressive, showing no tendency to heal. There had been a gradual increase in his pulmonary symptoms. He had noted tachycardia and palpitations, but denied cardiac pain. His appetite was good and weight loss had been slight.

Physical examination on admission to Bellevue on August 19, 1949 revealed a blind, well-nourished, well-developed Negro male who was markedly dyspneic and orthopneic with rapid, shallow respirations. His blood pressure was 170 systolic, 115 diastolic. Respirations were 40; temperature, 100 F; and pulse, 100. Over the anterior aspects of the legs and on the neck, nose, face, and trunk there were small round, papular lesions about 1 cm. in diameter, which were crusted, pigmented, and occasionally ulcerated. A generalized firm, nontender, discrete adenopathy was noted. Cardio-respiratory examination showed a symmetrical thoracic cage with a normal pulmonic-aortic diameter. There was dullness over the lower half of the chest, with hyperresonance over the upper half. The breath sounds were vesicular and coarse, with scattered moist rales and wheezes and a prolonged

expiratory phase. Liver and spleen were not palpable. No clubbing was evident. Slight ankle edema was noted.

Serial chest roentgenograms, beginning in 1947, showed a gradually increasing symmetrical, diffuse, nodular and streaking fibrosis. Bone roentgenograms were negative. Mediastinal adenopathy was not marked.

Laboratory studies: Blood count showed the following values: hemoglobin, 13.6 gm. per 100 cc.; erythrocytes, 4.6 million per cu. mm.; leukocytes, 4,500 per cu. mm., with eosinophilia ranging between 7 and 14 per cent. The erythrocyte sedimentation rate was 12 mm. per hour. Measurement of serum proteins gave the following A/G ratios: 4.5/1.7, 4.1/5.1, 3.3/3.6. A bromsulfalein test revealed 100 per cent dye retention at the end of thirty minutes and 20 per cent retention at the end of forty-five minutes. A phenolsulfonphthalein test showed impaired excretion of the dye. Urinary concentration and dilution tests were normal. Direct smear of the sputum was negative for acid-fast bacilli and a tuberculin test was negative up to .005 mg. of PPD. An initial electrocardiogram was interpreted as showing a vertical cardiac position and early right-axis deviation.

Course: The patient ran a low-grade fever between 99° and 100°F., with a persistent tachycardia. On bed rest, blood pressure returned to normal. He continued to bring up copious amounts of white, mucoid sputum with paroxysmal cough. There was little change in his tachypnea and dyspnea, which was marked on the slightest exertion. On September 12, 1949 venous pressure was 238 mm. of saline. The patient was begun on calciferol, 100,000 units three times a day, and dihydrotachysterol, 1 cc. a day, with no improvement. On September 29, 1949 the second pulmonic sound was accentuated; and short, systolic, apical, and pulmonary murmurs were present. The liver was palpable 3 finger-breadths below the costal margin but was not tender and the spleen was not enlarged. Pulmonary findings were essentially unchanged. There was 3 plus brawny edema of both lower extremities, but no scrotal or sacral edema. On October 2, 1949 the patient suddenly became unruly, incontinent, and completely disoriented. His talk was irrelevant and incoherent, and he developed visual and auditory hallucinations, but no localizing neurological signs. It was thought that these sudden changes were probably on the basis of cerebral anoxia, and on October 3, 1949 he was transferred to the Psychiatric Service.

On transfer he was in severe respiratory distress with Cheyne-Stokes respiration and a marked sinus arrhythmia. His blood pressure was 124 systolic, 84 diastolic; temperature, 101°F.; pulse, 100; respirations, 44. Moderate venous distention was present with the neck veins filling from below, bilateral dullness at both bases, bronchial breath sounds below the right scapula, and fine rales at the left base. Tenderness was noted in the right upper quadrant, although abdominal distention and flank bulging made examination difficult, with 4 plus pitting edema of the lower extremities and some sacral edema. Lumbar puncture was negative. An electrocardiogram showed increased right ventricular strain. During the next few days he showed considerable improvement on a regimen of ouabain, .25 mg. twice a day, diuretics, and oxygen. The respiratory rate remained elevated, but returned to normal rhythm. Tachycardia persisted. On October 6, 1949 his chest was clear, the edema had completely subsided, and the liver was no longer palpable. His sensorium showed marked clearing. The following day, without any change in his clinical picture, the patient suddenly died.

The pertinent findings of the pathologist on autopsy examination were as follows:

The body was that of a well-developed and nourished Negro male. Enophthalmos of the right eye was present, with marked corneal scarring obscuring the pupils and irides bilaterally. There was no cervical adenopathy; the left epitrochlear and both sets of inguinal nodes were enlarged. The chest was nonemphysematous. Nodules were palpable in both epididymi. No peripheral edema or clubbing was evident. The skin over the anterior surface of the thighs and legs contained numerous grayish papular and papulonecrotic nodules measuring from 3 to 6 mm. in diameter. Over the posterior nuchal area numerous confluent small papular lesions were found.

On examination of the abdominal cavity, the liver was down 5 cm. in the midclavicular

line and 10 cm. in the midline below the costal margin. The spleen was up under the costal border. The domes of both diaphragms were at the level of the fourth intercostal space. On opening the thorax, a generalized enlargement of the mediastinal and deep cervical lymph nodes was noted. The lungs were adherent to the anterolateral chest wall. No pleural fluid was present.

The heart was enlarged, weighing 515 gm. The epicardium was smooth and contained a moderate amount of fat. The myocardium was brown in color and somewhat paler than usual. The right ventricle was dilated and the columnae carnae and papillary muscles were hypertrophied. The right ventricle measured 5 to 7 mm. in thickness; the tricuspid valve, 14.5 cm.; and the pulmonic valve, 10 cm. in circumference. No atheromata were visible in the pulmonary artery. The left ventricle varied from 12 to 17 mm. in thickness; the endocardium was smooth throughout. The valve leaflets were delicate; and chordae tendinae, discrete. The circumferences of the mitral and aortic valves were 12.5 and 8.0 cm., respectively. On section through the interventricular septum, several discrete, faintly yellow tubercle-like lesions were noted, varying from 2 to 4 mm. in diameter. The coronary arteries showed minimal atheromatous changes.

On examination of the lungs, the pleural surfaces were smooth. Both upper lobes were firm, contracted, and crepitant. On section they showed an increased fibro-anthracotic consistence and numerous small, thin-walled bullous-like cysts were present which varied from 0.5 to 1. cm. in size and were prominent on the right side. The lower lobes were subcrepitant and the basilar portions were pink-gray in color. The fibrous consistence was less marked in the lower lobes, although a few smooth-walled bullae were present. The bronchi were normal. The hilar and tracheobronchial nodes were enlarged. The liver was enlarged and weighed 2,200 gm. It was mottled, brownish-gray in color, and of firm consistency. Several areas of irregular fibronodular density were present. The spleen was enlarged and weighed 240 gm. On section the corpuscles were prominent and gave the parenchyma a finely nodular appearance. Each kidney weighed 300 gm. and was of rather large size. The capsules stripped with ease, revealing a smooth, pale, brownish-red surface. Section showed a cortex easily demarcated from the medulla. Small yellow flecks were seen in the cortex and several pinhead-sized white nodules were present in the pyramids. Firm nodules were present in each epididymis.

Generalized lymphadenopathy of all the visceral lymphatic chains was found. Several enlarged deep cervical nodes were also identified. The nodal enlargement was variable, but in general measured 3 to 5 cm. in diameter. The nodes were firm and discrete with intact and nonfused capsules. On section they showed an increased fibronodular texture without caseation. One single caseous node was found in the tracheobronchial group.

Other gross findings were normal.

Microscopic Findings

Heart: A few focal aggregates of mononuclear cells were found within the epicardium, and increased hyalinization of the pericardial connective tissue. The muscle fibers within both ventricles were hypertrophied. The striking feature was the presence of miliary granulomata throughout the myocardium. These were occasionally confluent but were more often discrete and replaced the muscle fibers. A few were seen in the perivascular spaces; most were unrelated to blood vessels. Subendocardial lesions were noted. The granulomata were typically epithelioid, and contained a few lymphocytes. Many of the lesions showed areas of central breakdown indistinguishable from caseation necrosis. Numerous Langhans'-type giant cells were seen. Some of the granulomata were undergoing fibrosis, and many small fibrous scars were seen within the myocardium unrelated to the tubercles. Ziehl-Neelsen stain failed to reveal acid-fast bacilli.

Lungs: The granulomatous involvement of the lung presented a varied picture. All sections showed complete or almost complete replacement of normal tissue by densely confluent epithelioid tubercles containing numerous giant cells. In some sections a nodular pattern was formed by the confluent lesions, and in more involved areas no normal alveolar

structure was seen. Sections through the apex revealed cystic dilatation of the air space which was lined by granulomata. Many of the nodules were completely hyalinized and had a smattering of anthracotic pigment. These densely hyalinized nodules contained doubly refractive spicules. In one section a definite area of caseation-like necrosis was noted within an epithelioid tubercle. However, caseous lesions were very infrequent. The numerous giant cells were of both the foreign-body and Langhans' types. Their cytoplasm presented a varied appearance. Some showed cleft-like spaces which might represent a fibrous foreign body. Others had vacuoles which occasionally contained laminated eosinophilic material which sometimes appeared to be calcified. Some of the foreign-body material was doubly refractive. The granulomatous lesions showed a preference for the walls of the small bronchi and veins. They were noted in some areas to have completely replaced the bronchial wall, leaving the mucosa intact. Several of the veins showed a granulomatous endophlebitis, and in one a large polypoid, hyalinized mass protruded into the lumen of the vein. Ziehl-Neelsen stain through the caseous lesion failed to reveal acid-fast bacilli.

Liver: Many discrete and confluent epithelioid granulomata were noted in the liver. Some of these were periportal in site, others were unrelated to the portal spaces. The densely confluent lesions contained granulation tissue and had undergone considerable fibrosis and hyalinization. The hyaline masses were prominent in a few of the lesions. There was moderate fatty change of the parenchyma in the more involved areas. Central congestion and atrophy were noted throughout.

Spleen: The capsule was normal. Adjacent to many of the corpuscles discrete and occasionally confluent epithelioid granulomata were noted, some of which were undergoing fibrosis. The striking feature, common to all, was the presence of dense interlacing hyaline masses within the corpuscles. The red pulp was deeply congested.

Kidneys: The glomeruli and vessels were markedly congested throughout. In one small subcortical sector several hyalinized glomeruli were surrounded by lymphocytes. Interlacing bands of hyalinized connective tissue, similar to those described in the spleen, were noted within the lesion. No epithelioid or giant cells were seen.

Prostate and epididymis: The prostate was unremarkable. In the epididymis were numerous discrete and confluent epithelioid granulomata, many of which contained giant cells. No caseous areas were seen. One of the larger veins showed involvement of its wall by granulomatous tissue.

Lymph nodes, abdominal: Scattered throughout the node were numerous epithelioid tubercles some of which were undergoing fibrosis. Numerous giant cells were seen. No caseation was noted. There were interlacing hyaline bands similar to those seen in the liver and spleen.

Lymph node, mediastinal: At the periphery of the node were numerous epithelioid tubercles. Within this zone there was a dense hyalinized fibrous capsule containing considerable anthracotic pigment. The center of the node consisted of an amorphous, caseous mass with cholesterol clefts and early calcium deposition.

A final note on this case was added by Drs. Horace Shaffer and Marvin Kuschner, pathologists:

This was a puzzling case which may be variously interpreted. The clinical features are characteristic of sarcoid as are the distribution and type of morphologic lesions for the most part. The disturbing features are the presence of areas of caseation in the lung and heart and the unquestionably fibrocaseous node in the hilum. Since no organism was found in the lung and heart lesion, one may postulate, perhaps, that this is a nonspecific type of necrosis. Nevertheless, this type of lesion is certainly not characteristic of sarcoid. Although cultures of lung and caseous hilar node were negative for tubercle bacilli, guinea pig inoculation of the caseous hilar node was positive. The lymph node must therefore be considered tuberculous. Its relation to the present lesion is subject to question.

Of some interest is the presence of broad hyaline bands in the lymphoid tissue of the

spleen, the liver, and the lymph nodes. This material, described as paramyloid by some authors, is said to be related to high globulin levels.

Some of the fibrous whorled scars in the lung with anthracotic pigment and doubly refractive granules are undoubtedly sclerotic, although they play little part in the generalized pulmonary disease.

Final anatomical diagnosis: (*1*) Granulomatous lesion of lung, heart, kidneys, epididymi, skin and lymph nodes, either tuberculosis or Boeck's sarcoid; (*2*) tuberculosis of mediastinal lymph node; (*3*) hypertrophy of right ventricle: cor pulmonale; (*4*) fibrous pleural adhesions, bilateral; (*5*) emphysema of lungs; (*6*) chronic passive congestion of liver and spleen.

Several clinical findings in this case were also of particular interest. This was the only case in which the uveal tract involvement progressed to complete blindness. Although inoculation of the caseous mediastinal lymph node resulted in the development of tuberculosis in the inoculated guinea pig, this patient failed to react to .005 mg. PPD approximately six weeks before he died. The unequivocal presence of caseation necrosis and the positive guinea pig inoculation establish the concomitant diagnosis of tuberculosis, but the relationship between the two types of lesion depends upon one's individual conception of the pathogenesis of sarcoidosis and its relationship to tuberculosis. The cardiac lesions undoubtedly contributed towards the ultimate development of cardiac failure but the pulmonary fibrosis and well-established hypertension were also important factors in depleting this patient's cardiac reserve.

Case 45. J. R., a 29-year-old Negro male, was admitted to Bellevue Hospital on August 3, 1948 because of increasing dyspnea of five months' duration. In March 1948 he had been seen at another hospital when he complained of cough, sputum, night sweats, anorexia, and a 40-pound weight loss. Physical examination at that time revealed diffuse crepitant rales in both lungs. Three sputum concentrates were positive on direct smear for acid-fast bacilli after several other concentrates and gastric aspirates had been negative. A chest roentgenogram showed a diffuse bilateral parenchymal infiltration.

During his hospitalization the patient received a course of penicillin totaling 1,000,000 units and a course of streptomycin totaling 47.5 gm., without appreciable change in his clinical condition. On July 9, 1948 a total leukocyte count was 20,600 cells per cu. mm. with 74 per cent polymorphonuclear leukocytes, 8 per cent lymphocytes, 6 per cent monocytes, and 12 per cent eosinophils. On August 3, 1948 he was transferred to Bellevue Hospital with the diagnosis of advanced bilateral pulmonary tuberculosis.

On admission, the patient was febrile and appeared acutely and chronically ill. He was very dyspneic, orthopneic, and slightly cyanotic. Many moist rales were heard throughout both lung fields with some impaired resonance at the bases. There was a shotty posterior cervical adenopathy. Heart was negative except for marked accentuation of the second pulmonic sound. The liver and spleen were not enlarged.

Laboratory report: The erythrocyte sedimentation rate was 120 mm. per hour; the total leukocyte count, 20,000 cells per cu. mm. with an essentially normal differential except for a 5 per cent eosinophilia, which later disappeared. The tuberculin skin test was negative up to the second strength PPD. Many sputum examinations were negative by smear and culture for acid-fast bacilli, as were several gastric aspirates. Sputum culture for fungi was negative.

The patient continued to become increasingly dyspneic throughout his hospital course. He was febrile between 100° and 101°F. and was given oxygen almost continuously. On January 5, 1948 respiratory function tests showed a marked lowering of the arterial oxygen saturation with an observed basal saturation of 77 per cent while on 50 per cent oxygen by mask, and a fall to 26 per cent after breathing room air for five minutes. The predicted

percentage of residual air to total capacity was 19.8 per cent; the observed percentage was 60.7 per cent. The predicted maximum breathing capacity was 151; the observed was 81.4 liters per minute. The predicted total capacity was 5,600 cc.; the observed total capacity was 2,872 cc. The patient's general course was progressively downhill and he died on November 9, 1948.

Autopsy: Many dense fibrous adhesions were present in both the right and left pleural cavities, especially marked over the interlobular septum. All the lobes appeared identical and on their pleural aspects showed many minute nodules, whitish in color, measuring about 1.5 to 2 mm. in diameter. The lungs were very firm and had the consistency of liver. On section, nodules similar to those seen in the pleura were noted which protruded slightly above the cut surface, and no aerated lung could be identified. The color was brownish-

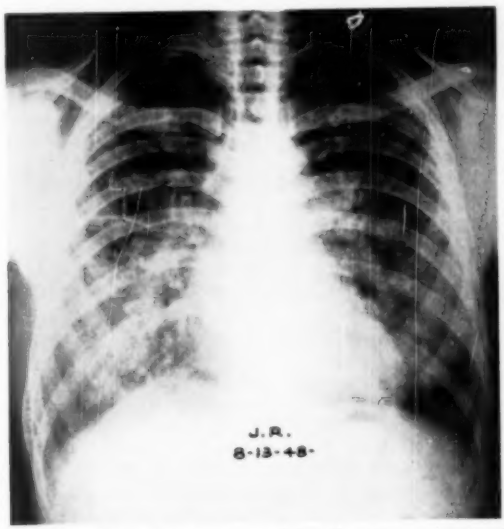

FIG. 12. Patient J. R. Bilateral extensive nodular fibrosis terminating in cor pulmonale and right heart failure.

gray and only on close inspection could the whitish nodules be made out. The apices of all the lobes except the right middle lobe showed numerous thin-walled cavities measuring from 2 to 9 mm. in diameter, without any evidence of caseous material or suppuration. The bronchi and pulmonary vessels were not remarkable. The heart showed some evidence of a prominent pulmonary conus and the right ventricle measured 3 to 7 mm. in thickness. The liver showed widely scattered whitish, minute nodules throughout the capsule and in the liver substance, and similar nodules were found in the spleen. The majority of the thoracic lymph nodes were moderately enlarged, some measuring 2 cm. in diameter. They were grayish-yellow in color, soft, and on section showed numerous white nodules, about 1 mm. in diameter, in the center as well as in the periphery. Nowhere was caseation necrosis present. The nodes involved were those of the anterior and posterior mediastinum, hilar, at the bifurcation of the trachea, periaortic, mesenteric, and one at the porta hepatis.

Microscopic examination of the lungs showed uniform involvement with a granulomatous lesion, primarily interstitial, consisting of epithelioid tubercles with numerous Langhans' giant cells and mild mononuclear cell infiltration. Surrounding fibrosis was considerable. In what alveoli could be seen, occasional squamous metaplasia of the wall was noted, but

in most places the alveoli were lined with cuboidal cells. They also contained numerous large mononuclear cells. No caseation was present and no acid-fast bacilli could be found. The small cavities found at the apices were mostly unlined clefts, but occasional areas of squamous metaplasia were present. Throughout the liver scattered epithelioid tubercles were noted, similar to those in the lungs. One similar tubercle was present beneath the cortex of one kidney. There were several tubercles in the testis, and all the lymph nodes showed innumerable tubercles without caseation. Acid-fast stains from lungs and lymph nodes were negative for acid-fast bacilli, as was a culture for acid-fast bacilli taken from the lung.

The final anatomical diagnoses were: (*1*) Diffuse granulomatous inflammation of the lungs, lymph nodes, liver, testes, and kidney; (*2*) myocardial hypertrophy of the right ventricle (cor pulmonale); (*3*) fibrous pleural adhesions, bilateral.

In view of the clinical course (including failure to respond to streptomycin), the pathological findings, and repeated cultures negative for tubercle bacilli, it is believed that this is a case of sarcoidosis and that the report of positive sputum from another hospital most probably represents a laboratory error or the presence of acid-fast saprophytes.

Case 46. A. R., a 24-year-old Negro female, was first seen at another hospital in October 1945 with the complaints of clouded vision of about one month's duration, slight cough, and a 17-pound weight loss. Sputum was slight, amounting to less than one-half cup daily.

Physical examination on admission was essentially negative except for a bilateral uveitis and marked tachycardia. Her chest was clear. A chest roentgenogram showed bilateral enlarged hilar nodes with patchy areas of infiltration scattered throughout both lung fields. There appeared to be two small blebs in the second right anterior interspace. She was transferred to Bellevue Hospital on October 14, 1945.

Examination on admission was essentially unchanged except for the finding of bilateral, discrete, nontender supraclavicular and inguinal nodes. Liver and spleen were not palpable. Roentgenograms of the hands and feet were negative. Many sputum examinations and three gastric aspirates were negative for acid-fast bacilli. The total leukocyte count was 8,000 cells per cu. mm. with 10 per cent eosinophils. The serum proteins were 7.7 gm. per 100 cc. with an A/G ratio of 4.1/3.6. The erythrocyte sedimentation rate was 30 mm. per hour. The tuberculin test, second strength PPD, was negative on two occasions.

During hospitalization the patient's temperature ranged between 99° and 100° F. Fine moist rales were heard at the right base. The uveitis showed some improvement on atropine and symptomatic therapy.

On November 7, 1945 biopsy of material from a cervical node was performed and the pathologic description is as follows: "The tissue consists of lymph node the structure of which is almost completely obliterated by the presence of innumerable tubercles which are well circumscribed and consist of epithelioid cells, multinucleated giant cells, and lymphocytes, lying in a connective tissue stroma. There are no areas of caseation necrosis present, but in the center of some of the tubercles is some eosinophilic granular material. Ziehl-Neelsen stain reveals no acid-fast bacilli."

A guinea pig inoculated with material from the node showed no gross or microscopic evidence of tuberculosis.

The patient was discharged on December 24, 1945. She remained in bed three months and gained about 20 pounds. Her eye symptoms receded and vision is now normal. As of July 1949 she was well and asymptomatic. A chest film taken July 26, 1949 shows regression of the hilar shadows together with clearing of the parenchymal infiltrate.

This case is one of the group which has shown complete clearing and the only case with ocular involvement which was wholly reversible.

Case 52. F. V., a 27-year-old white male, was admitted to Bellevue Hospital on February 4, 1948. In February 1937 he had noted the gradual onset of swelling and stiffening of the

fingers with cracking, widening, and shortening of the nails. This was followed a short time after by involvement of his toes, with considerable widening and swelling of the joints, which, however, returned to normal after a few months. At this time roentgenograms of his extremities showed marked irregular enlargement of the bones of his hands with thinning and cylindrical expansion of the cortex. Several bones showed evidence of previous marginal fractures, with considerable alteration of the joint surfaces and spaces, and a coarse architecture including multiple small irregular areas of rarefaction replacing the medullary trabeculae. Similar changes occurred in the terminal phalanges of the feet. A chest roentgenogram of April 12, 1937 showed accentuation of the hilar and pulmonary markings.

Physical examination revealed a well-developed white male with psoriatic lesions on the elbows, knees, and dorsum of the left foot. The tonsils were large and inflamed. Generalized lymphadenopathy was present. There was fissuring of the nails with diffuse enlargement of the phalangeal and metacarpal joints with limitation of motion and crepitation of some of the joints. The spleen was not palpable, although reported large by roentgenogram.

The tuberculin test was negative up to 0.1 cc. of OT. Biopsy of an epitrochlear node was compatible with sarcoidosis.

The patient was given calcium gluconate, Fowler's solution, and received heliotherapy and radiation to his extremities without improvement. He was afebrile and gained weight. Follow-up films of the chest and extremities in April 1938 showed no changes.

On admission to Bellevue Hospital on February 4, 1948 physical examination revealed no evidence of weight loss. The psoriatic lesions were still present; the tonsils were large, and palpable axillary and left epitrochlear lymph nodes were found. The chest was clear. The anteroposterior diameter was increased. Liver and spleen were both palpable. Diffuse swelling and discoloration of all the finger joints with severe clubbing were noted. A right dacryocystitis and mild conjunctivitis were present.

A roentgenogram of the chest showed scattered bilateral densities throughout both lung fields, most marked near the hila. Roentgenograms of the long bones were negative. Roentgenograms of the feet are reproduced (figure 2). One 72-hour sputum sample was positive on smear for acid-fast bacilli; three were negative, as was one gastric aspirate. Tuberculin tests with first and second strength PPD were negative. The erythrocyte sedimentation rate was 55 mm. per hour; serum calcium, 10 mg. per 100 cc.

On March 3, 1948 an epitrochlear node was biopsied and the report of the pathologist was as follows: "The sections reveal the presence of numerous miliary epithelioid tubercles disseminated throughout the substance. For the most part these are discrete although occasionally a few become confluent. Occasional Langhans' cells are seen, but no caseation necrosis. Ziehl-Neelsen stain fails to reveal the presence of acid-fast bacilli. There is a moderate focal deposition of acellular collagen in the interstices of the lymph cords." On March 12, 1948 a tonsillectomy was done and report of the pathologist on the tonsillar tissue is as follows: "Section reveals lymphoid tissue with a moderate increase in fibrous tissue. There are numerous nests of epithelioid giant cells, some of which contain astrocytic inclusion bodies. No areas of caseation are seen."

The patient's hospital course was uneventful. He was asymptomatic and afebrile. There was no change in serial films. An eye consultant believed that the eye lesions were still in the early stages.

Reviewing the two biopsy specimens taken at an eleven-year interval, the morphologic appearance of the two sections is almost identical. Clinically and pathologically, the disease appeared to have shown no change during this time. This is the only case in this series in which tonsillectomy was performed.

THERAPY

The treatment of sarcoidosis, which of necessity remains entirely on an empirical basis, has been disappointing. The natural course of the disease is so

variable that the beneficial results claimed for any specific therapeutic agent must be interpreted with extreme caution. Many different agents have been employed, but it is believed no convincing evidence exists that any one of them has altered the course of the disease or prevented the development of related complications. In each individual, sarcoidosis seems to follow a predestined path from which it cannot be diverted.

Of the many therapeutic agents which have been tried in this group of patients, none had appreciable effect. In 6 patients with massive hilar adenopathy, deep X-ray therapy was directed over the anterior mediastinum with negative results, or followed by changes which were entirely compatible with the natural course of the disease. One patient in this group, for example, showed bilateral regression of the hilar adenopathy although radiation was directed over one side of the mediastinum only (figure 4). Although certain authors (65) believe that radiation may have beneficial effects, the results in this series corroborate the findings recently published by Donlan (66) who treated 11 cases of sarcoidosis with deep radiation therapy without clinical improvement. The value of radiation therapy in Boeck's sarcoid is only in the differential diagnosis between radio-sensitive and radio-resistant mediastinal masses when the differential diagnosis may lie between this disease and one of the radio-sensitive lymphomas. No success was observed in preventing the development of the ocular complications, possibly because in all patients treatment was begun following the development of irreparable damage and irreversible anatomical changes.

Little was gained by therapeutic measures in preventing the development of pulmonary tuberculosis or extensive pulmonary fibrosis. It has been the custom to recommend a period of bed rest for those patients with pulmonary sarcoidosis who have been hospitalized on the Chest Service. Reviewing the 13 cases which developed active pulmonary tuberculosis, it was found that 3 were given no bed rest at all following the establishment of the diagnosis of sarcoidosis. Five patients were on bed rest for periods ranging from one to five months, and the remaining 5 patients were given bed rest for more than five months. In this latter group one patient developed clinically active tuberculosis after a period of bed rest of 18 months and another after a period of bed rest of 29 months. Although this is a small group, it is highly suggestive that bed rest has no prophylactic value in preventing the development of tuberculosis. It was often difficult to ascertain from the records available exactly how strict a regimen of bed rest was maintained by these patients. It is fair to assume that a routine of at least modified bed rest, or of markedly limited ambulatory activity, was followed by the majority of this group.

The greater number of patients developing active tuberculosis were hospitalized for varying periods of time in tuberculosis hospitals or sanatoriums where there was a long period of exposure to high concentrations of tubercle bacilli. The question legitimately arises whether the development of tuberculosis might be related to this heavy exposure to tubercle bacilli by patients who were predominately nonreactors to standard tuberculin tests and thereby generally considered to be more susceptible to the disease.

Accordingly, the incidence and average length of sanatorium care was compared in the two groups of patients. Nine, or 70 per cent, of the patients who developed active tuberculosis had been given sanatorium care, presumably in close contact with active cases of the disease, for an average period of 6.2 months. Among the 35 remaining patients who during an adequate period of follow-up did not develop tuberculosis, 18, or 51 per cent, had been given sanatorium care for an average period of 5.2 months. Considering the small number of patients involved, the difference between 70 per cent and 51 per cent is probably not of statistical significance. It does little to substantiate the theory that the development of tuberculosis in these cases of sarcoidosis was the result of an exogenous infection from an environment where there is a high concentration of tubercle bacilli. However, this is such an important consideration that further investigation along these lines should be carried out.

In a similar manner the development of pulmonary fibrosis does not appear to be influenced by periods of bed rest. Many of the clearing cases were either given short periods of bed rest or none at all. Conversely, 4 patients developed progressive pulmonary fibrosis despite bed rest varying from 11 to 18 months.

Experience with specific antibiotic therapy has been limited to 2 patients in this group. One patient was given a full course of Promizole with no change in the over-all picture. The pulmonary lesions, however, had probably already reached an irreversible stage when therapy was initiated. A second patient was given a prolonged course of penicillin and a course of streptomycin totaling 47.5 gm., with no clinical response and eventual death from right heart failure secondary to extreme pulmonary fibrosis. As with the preceding patient, however, therapy was probably begun after irreparable anatomic damage had occurred.

Since it is generally conceded that sarcoidosis is an infectious disease, although the specific organism has not been demonstrated, it would seem that early treatment with the newer antibiotics, such as streptomycin, aureomycin, chloromycetin, and others should be the proper therapeutic approach towards this disease, in the hope of not only altering the apparently inevitable outcome but also of perhaps helping to clarify the etiology.

ETIOLOGY

Probably no issue in the field of internal medicine has aroused more interest and controversy in the medical literature during the past twenty years than the question of the etiology of sarcoidosis. The majority of writers, for reasons which are inferential and circumstantial, favor some form of the tubercle bacillus as the etiologic agent. Other students of the disease believe that it may be the result of a number of different causes and there are those who, to quote Pinner (31), hold, "The most prudent, although not the most fertile attitude," that the etiology is unknown. Many of the arguments offered are highly theoretical, dogmatic, and often based on evidence which has been interpreted and selected to substantiate the writer's preconceived ideas. The identical clinical, laboratory, and anatomic findings are quoted as evidence for and against the tuberculous

etiology. It is not within the scope of this article to review all of the evidence on both sides of the question. A detailed and objective summary of the prevailing theories has been included in Freiman's (8) recent review of the disease. It seems of value, however, to comment briefly on some of the evidence presented by both sides.

Probably the strongest argument against a tuberculous etiology has been the failure in an overwhelming majority of cases to recover tubercle bacilli, either by culture or by animal inoculation from biopsy or autopsy material in patients who present the clinical and laboratory features of sarcoidosis without complicating overt active tuberculosis. None of the scattered reports of the recovery of tubercle bacilli holds up on critical objective examination. Usually the claims are based on the presence of acid-fast bacilli on smear and are not verified by further cultures or animal inoculation. The possibility of laboratory error or the presence of nonpathogenic acid-fast saprophytic rods are extremely important considerations which are invariably not mentioned or are minimized, but which should be taken into consideration in the evaluation of findings on smear technique alone. The case recently presented by Schaumann and Hallberg (67) is a typical example. One theoretical explanation of this consistent failure is that in sarcoidosis the tubercle bacillus assumes a filterable or nonacid-fast form or else changes its cultural characteristics. Another highly theoretical explanation is that the organisms are present in the early lesions but rapidly disappear as the lesions mature. This explanation is largely based upon a single controversial and often quoted case reported by Kyrle (68) who claimed to have recovered acid-fast bacilli in early lesions which failed to cause tuberculosis when injected into guinea pigs, but who was unable to find these organisms as the lesions in his patient became older. These arguments need much further confirmatory support before they can be accepted without reservation.

In addition to consistent failure to cultivate tubercle bacilli from these lesions, it has been found that emulsions from sarcoid lesions do not cause tuberculosis when injected into experimental animals (69). They may, however, produce sarcoid-like reactions in humans with sarcoidosis, a phenomenon which forms the basis for the Kveim test (7). It has been found that this reaction is not specific (70), and further studies may indicate that it results from some type of "altered tissue reactibility on the part of the host" (8). In one recently reported case (71), injection of sarcoid material into guinea pigs produced sarcoid reactions and sensitized the animal to tuberculin. Acid-fast bacilli were demonstrated on smear, but failed to grow on culture. Although Pinner believed that insistence upon the fulfillment of Koch's postulates oversimplifies the problem of the etiology of sarcoidosis, these negative bacteriologic results are strong arguments against a tuberculous etiology.

Among the most cogent arguments for a tuberculous etiology is the high incidence of complicating tuberculosis and the frequency of this disease as the cause of death, although at least one writer (72) believes that from the study of autopsy material it is doubtful if tuberculosis is more often the cause of death in patients in this age group than in patients without sarcoidosis. This may be

true among Negroes, in whom the mortality from tuberculosis among young adults is extremely high. If one accepts the hypothesis that sarcoidosis is a transitional form towards caseating tuberculosis, this development is easy to explain. However, the possibility of an added superinfection cannot be easily or entirely ruled out for reasons previously noted. It is also possible, as suggested by Woods and Guyton (73), that extensive pulmonary fibrosis and impaired function may in some way predispose to the development of pulmonary tuberculosis, perhaps in a manner analagous to silicosis. It has also been suggested (74) that a sarcoid lesion may impinge upon a partially healed tuberculous focus to cause destruction of the fibrous capsule and liberation of tubercle bacilli. This theory is not inconsistent with observed pathologic findings as summarized by Mallory (49), but is highly theoretical and needs anatomic confirmation.

The high incidence of nonreactors to the tuberculin test undoubtedly has some relationship to the etiology, but the relationship is not clear. It does not always imply freedom from a primary tuberculous infection, since roentgenographic and autopsy findings in nonreactors have often demonstrated calcific or fibrocalcific foci, presumably in most instances a healed primary tuberculous infection. A primary tuberculous infection antedating the onset of sarcoidosis has recently been observed clinically (75). In addition, a not insignificant number of patients with sarcoidosis exhibit a positive tuberculin reaction, indicating a past tuberculous infection. It is also true that evidence of a past tuberculous infection may be present with a negative tuberculin test, indicating loss of sensitivity or, less likely, the absence of allergy that was never established.

Assuming that the sarcoid tubercle represents the ultimate of a "productive" type of response to tubercle bacilli attributed to an extremely high innate host resistance (somewhat difficult to explain in view of the accepted low resistance of the Negro race to tuberculosis), this nonreactivity has been explained by some in terms of a "positive anergy." This theory, first proposed by Jadassohn, has received support from Schaumann (43), who says "It will doubtless be recognized that infection by the tubercle bacillus may carry not only hypersensibility as regards tuberculin and other tuberculo-toxic products, but also under certain circumstances, which still defy detection, an asensitivity with regard to the said substance." Lemming (76) also states "we cannot entirely deny the possibility of an allergic organism being also tuberculin anergic."

This theory is a highly theoretical one with little, if any, factual basis. Another more likely possibility, which requires further investigative research, is that for some reason these individuals are constitutionally unable to produce circulating antibodies in response to the introduction of a foreign antigen. Lemming has found that a high proportion of tuberculin-negative sarcoid patients fail to become tuberculin-positive following inoculation with BCG. This theory, however, does not hold when applied to patients with sarcoidosis who exhibit a positive tuberculin skin test. Whether this anergy is specific for the tubercle bacillus or its products, or includes anergy to other allergins, is not known at present. No large-scale study of this problem has been attempted. Brooke and

Day (77) have shown that patients with sarcoidosis fail to react to different mycobacterial tuberculins unless they have positive tuberculin skin tests, in which event they may show a positive reaction. Other more recent studies (78) have shown that these patients are nonreactors to antigens which produce re-

TABLE 10

Correlation between Tuberculin Sensitivity and Pertinent Clinical Data

PATIENT	PAST HISTORY	TUBERCULOSIS CONTACT	PRIMARY COMPLEX	PLEURAL CHANGES	TUBERCULIN TEST	ACTIVE TUBERCULOSIS	TUBERCULIN TEST FOLLOWING ACTIVE TUBERCULOSIS
E. A.				Yes	Positive		
V. B.	Pleurisy with effusion			Yes	Positive	Yes	Positive
J. B.					Negative	Yes	Positive
M. B.			On autopsy		Negative		
H. B.				Yes	Positive		
D. B.		Yes	Yes	Yes	Negative	Yes	Positive
L. C.			Yes		Positive		
E. C.			Yes		Negative		
P. C.					Positive	Yes	Positive
E. C.					Negative	Yes	Positive
T. D.			Yes	Yes	Positive	Yes	
A. D.					Negative	Yes	Positive
E. A.			Yes		Positive		
B. F.					Negative	Yes	Positive
O. G.		Yes			Negative	Yes	Positive
C. J.	Pleurisy			Yes	Positive		
A. K.		Yes	Yes		Positive		
F. McE.				Yes	Negative		
D. M.				Yes	Negative	Yes	Positive
B. M.		Yes			Positive		
B. M.				?	Positive		
K. M.	"Dry pleurisy"		Yes		Negative		
E. Q.					Positive		
B. S.					Negative	Yes	
C. S.		Yes	Yes		Positive		
F. S.		Yes			Negative		
I. W.					Positive		
L. W.					Negative (.00002 mg. PPD)	Yes	
A. W.					Negative	Yes	Positive

actions in a large percentage of patients with tuberculosis. Whether this anergy is nonspecific can be determined only by testing with the appropriate antigens large numbers of patients with sarcoidosis in areas in which coccidiosis and histoplasmosis are endemic.

In table 10 an attempt has been made to correlate tuberculin sensitivity with

the past history, history of tuberculous contacts, and other clinical data in this group of patients. There was little correlation, for example, between tuberculin sensitivity and the presence of a calcified pulmonary focus or a history of tuberculous contacts, or between tuberculin sensitivity and the later development of clinically active tuberculosis. The only constant finding was the conversion of a nonreactor to a reactor in those tuberculin-tested nonreactors who later developed overt tuberculosis. This is consistent with the theory that caseation is a manifestation of allergy.

The case against a tuberculous etiology would be much stronger if it were not for the well-known fact that under certain conditions the pathologic response to virulent tubercle bacilli, not only in tuberculosis induced in experimental animals but also in the naturally occurring disease in humans, may morphologically be indistinguishable from sarcoidosis. Both the caseating and noncaseating tubercles are often found side by side in cases where there is no question about the diagnosis of tuberculosis. Recently, Warfvinge (79) has reported a case of sarcoidosis complicated by the later development of overt tuberculosis in which an intracutaneous autoinoculation with tubercle bacilli recovered from the sputum produced a sarcoid-like response but from which tubercle bacilli could not be recovered. Because of the similarity of the morphologic pattern seen in these two diseases, it is not believed that the two can be differentiated on histologic grounds alone.

The juxtaposition of the two types of lesions does not necessarily imply a common etiology any more than does the concomitant presence of the lesions of tuberculosis and Hodgkin's disease or silicosis. The histologic appearance of the lesions of sarcoidosis are simply variants of the morphologic response common to many granulomatous diseases and is nonspecific, even to the presence of the inclusion bodies which were once thought to be a specific part of the histologic picture. It has been demonstrated experimentally (80) that tubercle bacillus lipins produce a sarcoid type of pathologic reaction when injected into guinea pigs, but that an identical reaction, even to the appearance of both the Langhans' giant cell and the so-called "foreign-body" type of giant cell, is caused by the injection of grass and colon bacilli lipins. Similar responses have been noted following injection of the bovine bacillus (81) in which it was found that the degree of caseation and ease of recovery of the bacilli were in direct proportion to the virulence of the injected organism, an observation lending support to the theory that the disease is caused by the bovine bacillus.

The nonspecificity of the histologic response has been used as a strong argument by those who believe that the disease may be caused by a variety of etiologic agents and who cite as examples the close histologic similarity between the lesions of sarcoidosis and the lesions produced by syphilis, leishmaniasis, tuberculoid leprosy, brucellosis, certain fungus diseases, foreign bodies, and beryllium granulomatosis. There may also be certain clinical similarities which, however, are generally overemphasized; whereas the differences, both clinical and pathologic, are not stressed. Beryllium disease of the lungs, for example, has been labeled by one author (82) "pulmonary sarcoidosis." The morphologic resemblance of the cutaneous lesions to sarcoidosis has also been noted (83, 84).

There are definite differences between the clinical course of the two diseases (85) and differences have also been noted in the microscopic appearance of the lesions (86, 87). Since there is still a lack of unanimity concerning the histologic appearance of beryllium granulomatosis and since it is a relatively new disease entity, the clinical pattern of which has not yet been completely established, it is possible that the disease in a not inconsiderable number of patients has in the past been misdiagnosed as sarcoidosis. A close morphologic and clinical resemblance exists between sarcoidosis and tuberculoid leprosy (88, 89) although the differences are such that a differential diagnosis in most cases should not be difficult. Brucellosis resembles sarcoidosis in the not infrequent complication of iridocyclitis (72) and the occasional appearance of pulmonary changes (90).

The extrapulmonary distribution of lesions in sarcoidosis is highly suggestive of a hematogenous dissemination and the incidence of different organ involvement parallels that of any chronic disseminated disease. There are, however, certain differences in the distribution of lesions when compared with the distribution seen in chronic hematogenous tuberculosis. Myocardial, parotid, and lacrimal gland involvement are infrequent in cases of disseminated tuberculosis, but common in sarcoidosis. Conversely, involvement of the pleura, peritoneum, pericardium, and meninges are not infrequent complications of disseminated tuberculosis, but are unusual manifestations of sarcoidosis. Whether these differences may be related to high host resistance and/or low virulence of the etiologic organism is purely speculative. The microscopic distribution of lesions is also said to differ; the hepatic lesions (91), for example, being most numerous in the portal areas, the reverse being claimed for hematogenous tuberculosis.

On an epidemiologic basis differences exist also between this disease and tuberculosis. The infrequent occurrence of sarcoidosis in siblings, the low incidence of contact cases with active tuberculosis, and the failure to observe an increase in the disease paralleling the rise of tuberculosis in areas ravaged by the recent war are all arguments used by those who doubt a tuberculous etiology. These observations, in addition to the fact that sarcoidosis fails to respond to bed rest and other measures usually effective in the therapy of pulmonary tuberculosis, have recently been stressed by both Michelson (13) and Snapper (14).

In an impartial review of the clinical and experimental evidence at hand, it seems that one must be forced to admit that the etiology of sarcoidosis at the present time is unknown. One cannot deny that there is some relationship, as yet incompletely defined, between this disease and tuberculosis. It is doubtful if further clinical studies of this type will aid in clarifying the etiology, but investigations should be directed toward studies which may elucidate the problem of allergy and resistance to the tubercle bacillus in this group of patients. It is also believed that efforts towards early empirical treatment and attempts to discover more subtle and profitable cultural and inoculation techniques may aid in arriving at a solution of the problem of the etiology of this disease.

SUMMARY AND CONCLUSIONS

This report details the experience gained in a clinical study of 52 cases of sarcoidosis, together with a review of the pertinent literature. Boeck's sarcoid

is a chronic, infectious, granulomatous disease, showing a predilection in this country for young adults of the Negro race. The etiology of sarcoidosis remains obscure. There is a close relationship between sarcoidosis and tuberculosis, although the exact nature of this relationship is not clear at present. No direct evidence exists that Boeck's sarcoid is caused by the tubercle bacillus. While not denying the possibility that further investigative work may prove that the proponents of a tuberculous etiology are correct, at the present time the available evidence is too contradictory and inconclusive to warrant drawing any conclusions regarding etiology. Although in instances the disease may show complete regression, the benignity of sarcoidosis has been greatly overemphasized. The eventual outcome of this disease and the development of directly related complications are uninfluenced by any presently employed methods of therapy.

The related mortality in this series has been almost 20 per cent; an additional 13 per cent of the patients have developed clinically active tuberculosis during the period of follow-up. These figures do not include the high percentage of patients with irreversible ocular and pulmonary damage. The term "benign lymphogranulomatosis" is misleading by its implication and probably should be abandoned.

SUMARIO Y CONCLUSIONES

El Sarcoides de Boeck: Reseña Basada en el Estudio Clínico de Cincuenta y Dos Casos

En esta comunicación expónese lo aprendido en el estudio clínico de 52 casos de sarcoidosis, junto con un repaso de la literatura pertinente. El sarcoides de Boeck es una enfermedad granulomatosa infecciosa crónica, que revela en los Estados Unidos predilección hacia los negros jóvenes. La etiología permanece en la oscuridad. Existe íntima relación entre la sarcoidosis y la tuberculosis, aunque la precisa naturaleza de esa relación no ha sido aun aclarada. No hay datos directos de que el sarcoides de Boeck sea ocasionado por el bacilo tuberculoso. Sin negar la posibilidad de que nuevas investigaciones demuestren que están en lo cierto los partidarios de la etiología tuberculosa, los datos disponibles en la actualidad son demasiado contradictorios y vagos para justificar conclusiones relativas a la etiología. Si bien la afección puede mostrar regresión total en algunos casos, se ha exagerado considerablemente la benignidad de la sarcoidosis. El desenlace final de la enfermedad y la aparición de complicaciones relacionadas directamente con la misma no son afectadas por ninguno de los métodos terapéuticos utilizados hoy día.

En la serie repasada la mortalidad ha sido casi de 20 por ciento; y otro 13 por ciento de los casos ha manifestado tuberculosis clínicamente activa durante el período de observación subsiguiente. Estas cifras no comprenden el elevado porcentaje de enfermos con lesiones reversibles en los ojos y pulmones. El término de "linfogranulomatosis benigna" se presta a confusión por lo que implica y debe probablemente ser abandonado.

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GENETIC STUDIES ON THE DEVELOPMENT OF RESISTANCE TO NEOMYCIN AND DIHYDROSTREPTOMYCIN IN MYCOBACTERIUM RANAE[1,2,3]

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INTRODUCTION

It has been suggested by Waksman and his colleagues that the quantity production of a newly discovered antibiotic and its extensive medical use should await rigorous comparison with established chemotherapeutic agents by a variety of evaluative criteria (1). Among these criteria are the activity of the new antibiotic against strains of bacteria resistant to established agents and the degree or rapidity with which bacterial resistance becomes established. Analysis of the development of resistance can be made by the techniques of microbial genetics. These afford a quantitative measure of the emergence pattern of various levels of resistance, the *in vitro* conditions necessary for resistance to appear, and the absolute probability (mutation rate) that defines the origin of a resistant variant from a sensitive strain. Because of the apparent promise of neomycin as an antimycobacterial agent, it has seemed essential to study the origin of resistance to this antibiotic. Historical perspective and proved value in the treatment of tuberculosis make streptomycin the logical standard of comparison.

A crude preparation of neomycin was reported by Waksman and his associates to be more effective than streptomycin against many gram-negative and gram-positive bacteria, including *Mycobacteria*, both pathogenic and saprophytic. The protective dose of neomycin for mice infected with *Staphylococci* and *Salmonellae* was found to be about one-twentieth to one-fiftieth of the toxic dose, depending on the nature of the particular lot of material and the degree of purity. When instilled into the conjunctival sac of the rabbit in a concentration of 1,500 units per ml. for 30 minutes, Waksman, Frankel, and Graessle found the crude preparation of neomycin produced only a transient irritation with no delayed toxic signs in an observation period of seven days (2).

The promise of neomycin as a therapeutic agent is substantiated by the present investigations on the origin of resistance. On the basis of genetic studies by Demerec (3, 4) and those described herein, we will adopt the convenient expedient of defining the genetic origin of resistance as (*1*) one-step resistance, (*2*) obligatory multiple-step resistance, and (*3*) facultative multiple-step resistance.

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[2] This study was made possible by a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

[3] Presented before the Medical Section, as part of the symposium on *Laboratory and Other Basic Research*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

One-step resistance is an all-or-none process, exemplified by the conversion of sensitive *Escherichia coli* to complete phage resistance by a single mutation. The mutational step may produce resistance to more than one class of bacteriophage (5).

Obligatory multiple-step resistance is a very common pattern represented by the development of comparative tolerance in *E. coli* to penicillin (3) or to nitrogen mustard (6) after a series of transfers in increasing doses of the toxic selective agent. A cumulative series of small incremental steps appears to be involved.

Facultative multiple-step resistance is characteristic of the origin of resistance to streptomycin and represents a combination of the other two types. By this scheme bacteria either may, or may not, develop complete immunity to the effects of streptomycin by means of a single mutation. When complete resistance does not arise in a single step the mutants are defined as low grade, or intermediate; and presumably find their counterpart in the first selective steps in systems of obligatory multiple-step resistance. In either system, mutants of intermediate grade may go on to the development of complete resistance by the occurrence of additional mutation acted upon by the selective effect of the environment.

These distinctions have been made at some length because they are of the utmost clinical importance. Only where the development of resistance is by way of an obligatory multiple-step process can the development of resistant strains be held in check by the use of high concentrations of an antibiotic. Such is the case with penicillin. With streptomycin the facultative multiple-step resistance pattern renders the ultimate development of strains uninhibited by this antibiotic a relatively probable event, often with unfortunate therapeutic consequences. The future value of neomycin, therefore, depends in no small degree on which of the three resistance systems best describes the manner whereby cells become unsusceptible to its antibacterial effects.

A certain amount of controversy exists concerning the toxicity of neomycin for humans. Progress in the purification process may be expected to produce less toxic fractions, but at a possible sacrifice in antibacterial activity. Simultaneous administration of other chemotherapeutic agents may perhaps reduce the required dosage to safer levels. In anticipation that combined therapy will be used, we have studied the effects of neomycin in combination with dihydrostreptomycin. The significance of combinations of agents in preventing the origin of resistant strains has been discussed by Bryson and Grace (7), Klein and Kimmelman (8), and many others. The attendant advantages of additive or synergistic action add to the interest attending studies of multiple chemotherapy.

MATERIALS AND METHODS

The organism used for these experiments was a culture of *M. ranae* obtained from William Steenken, Jr. of the Trudeau Laboratory, New York. Like most, if not all, so-called pure cultures, it consisted of a number of biotypes in which existence could be demonstrated by exposing large numbers of cells to various selective agents. For experimental purpose the cells were grown in Petri plates containing nutrient agar with 5 per cent glycerol and 0.1 per cent asparagine.

Stocks were prepared in aerated nutrient broth containing 0.1 per cent Triton A-20 (9). After growth at 37°C. for two to four days a titer of about 10^9 cells per ml. was attained.

Neomycin, lot 116, provided by Chas. Pfizer & Co., Inc., was used. The original concentration of 180 units per mg. was diluted in demineralized water to give 10^4 units per ml. From this dilution the lower concentrations were prepared. The dihydrostreptomycin sulfate was lot 651 of Merck & Co., Inc. made to a concentration of 5×10^4 γ per ml. in saline and refrigerated. The potency of stock solutions was checked periodically by bioassay with *M. ranae*.

In asparagine glycerol agar, all or the majority of cells formed colonies after

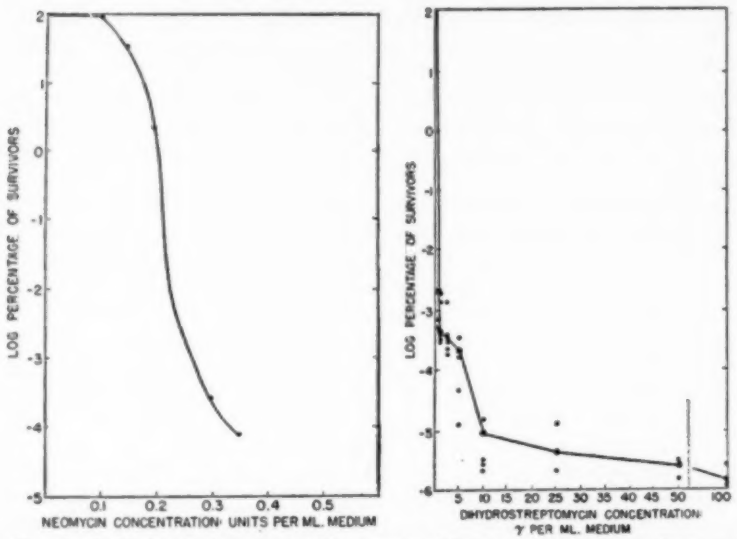


FIG. 1. (Left) Survival curve for *M. ranae* in different concentrations of neomycin, representing an average of five independent experiments in asparagine glycerol agar.
FIG. 2. (Right) Survival curve for *M. ranae* in different concentrations of streptomycin.

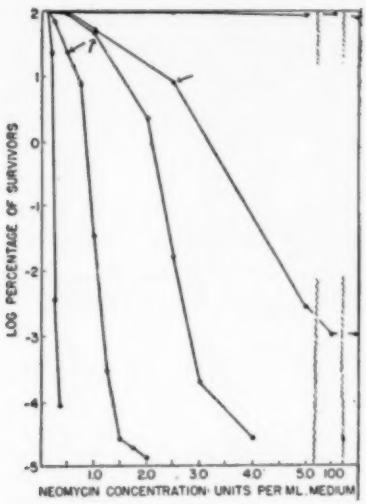
five to six days' incubation at 37°C., except where otherwise indicated. Tests showed that additional incubation to a total period of fourteen days gave a negligible change in results. Controls with sensitive *M. ranae* were run in all experiments to be certain that no extraneous factors were responsible for the increased survival of resistant cells in the presence of the antibiotic.

EXPERIMENTAL

Pattern of Development of Resistance

One unit of neomycin per ml. of asparagine glycerol agar was sufficient to inhibit the growth of approximately 10^8 sensitive *M. ranae* seeded into a Petri plate. Figures 1 and 2 show that in comparison a concentration of 100 γ of dihy-

drostreptomycin per ml. was inadequate to prevent the survival of a few individual cells, the presence of which is subsequently revealed by colony formation. The survival curves indicate that the majority of bacteria are sensitive to a narrow threshold concentration of the two antibiotics, as is seen by the sharp breaks. Colonies growing on plates containing 0.5 unit of neomycin per ml. were emulsified, diluted in sterile broth, and streaked on plain asparagine glycerol agar. After incubation, mutant stocks were obtained by subculture from the streaks, usually two stocks being established from each plate. A typical survival



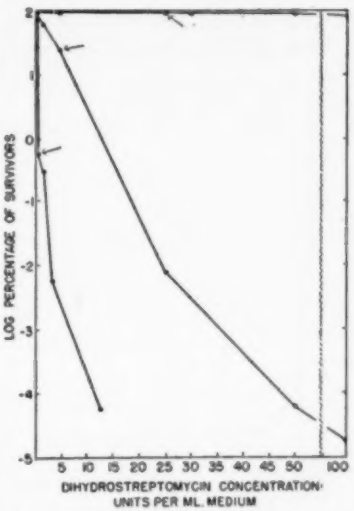


FIG. 3. (Left) Stepwise build-up of resistance to neomycin in *M. ranae*. First from left, survival curve of the original strain; second, survival curve of the first-step resistant strain isolated from a colony of the original strain growing on the concentration indicated by the arrow. The other curves are of second-, third-, and fourth-step resistant strains isolated from colonies growing on the concentrations indicated by the arrows.

FIG. 4. (Right) Survival curves of three different first-step selection strains resistant to dihydrostreptomycin, showing the great variability in degree of resistance. Each strain was isolated from a colony of the original strain developed on the concentration of dihydrostreptomycin indicated by the arrow.

curve of these first-step resistant strains is shown in the second curve from the left in figure 3. It was now necessary to use 2.5 units of neomycin per ml. to inhibit the growth of an inoculum of about 10^8 cells for the five-day observation period. Figure 3 reveals that increasing quantities of neomycin were needed to check the exponentially increasing degree of resistance of third- and fourth-step resistant mutants. Inspection of the curves from left to right shows each stock to be more resistant than its preceding parent strain. The arrows indicate the parental derivation of each succeeding culture and, together with the curves, give a resistance pattern very similar to that described by Demerec for the origin

of penicillin resistance in *Staphylococcus aureus* (3). All fourth-step resistant mutants isolated from plates containing 5, 10, 25, 50, and 100 units of neomycin per ml. showed complete resistance to 200 units.

In contrast, the data in figure 4 show that in the first-selection step all degrees of resistance to dihydrostreptomycin may be obtained, ranging from slightly resistant to fully resistant. No great difference exists between the number of survivors at the 25- and 100-microgram level.

Additive Effect of Neomycin and Dihydrostreptomycin

Because of the toxicity of neomycin and dihydrostreptomycin, some interest may be attached to the effects of combining these two substances with the pos-

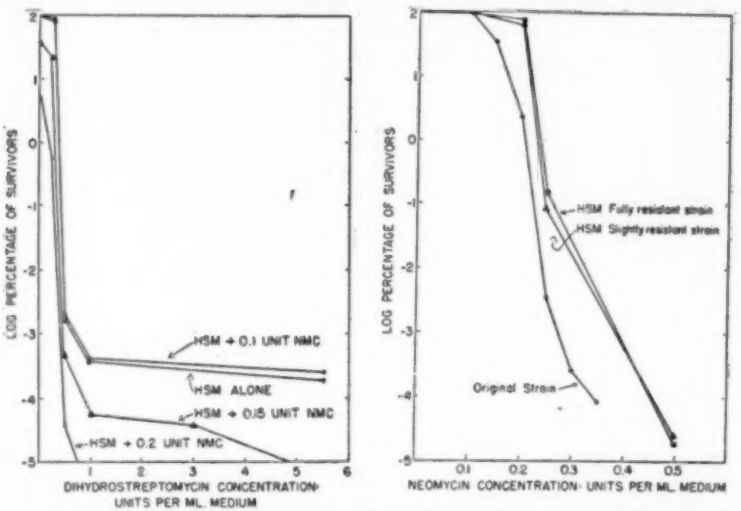

LOG PERCENTAGE OF SURVIVORS
HSM + 0.1 UNIT NMC
HSM ALONE
HSM + 0.05 UNIT NMC
HSM + 0.2 UNIT NMC
DIHYDROSTREPTOMYCIN CONCENTRATION· UNITS PER ML. MEDIUM
LOG PERCENTAGE OF SURVIVORS
HSM Fully resistant strain
HSM Slightly resistant strain
Original Strain
NEOMYCIN CONCENTRATION· UNITS PER ML. MEDIUM

FIG. 5. (Left) Survival curves for the original strain of *M. ranae* on various concentrations of dihydrostreptomycin (HSM), with and without the addition of neomycin (NMC).

FIG. 6. (Right) Effect of varied concentrations of neomycin on a sensitive strain of *M. ranae*, compared with strains resistant to dihydrostreptomycin (HSM).

sibility of reducing the component dosage level. Evidence showed that partially effective quantities of neomycin and dihydrostreptomycin combined *in vitro* exhibited a higher inhibitory action on *M. ranae* than either of them used alone (figure 5). If the concentration of either antibiotic, however, was below its individual effective threshold, it was of no value in combination. Therefore the combined effect of the two antibiotics appears to be additive rather than synergistic.

Cross Resistance

Waksman, Hutchison, and Katz have observed that neomycin is as effective in acting upon a streptomycin-resistant strain of M. 607 as it is in inhibiting

the sensitive strain (1). They did not produce a highly neomycin-resistant strain.

The writers' data indicate that strains of *M. ranae* either slightly or fully resistant to dihydrostreptomycin show slight cross resistance only at neomycin concentrations of 0.2 to 0.5 units per ml. of asparagine glycerol agar. Above this level all dihydrostreptomycin-resistant strains show the same sensitivity to neomycin as does the original wild-type strain; thus, figure 6 shows that one unit of neomycin is equally inhibitory to the growth of dihydrostreptomycin-resistant and dihydrostreptomycin-sensitive strains of *M. ranae* over the five-day observation period. No attempt has been made to record colony count for longer incubation periods.

In the reciprocal situation, neomycin-resistant strains of various grades of resistance are as sensitive to dihydrostreptomycin as the original strain, except for a slightly greater viability of fourth-step neomycin-resistant bacteria in low concentrations of dihydrostreptomycin (0.5 γ per ml. of asparagine glycerol agar).

TABLE 1

Number of Colonies Developed on Asparagine Glycerol Agar Containing 100 Units of Neomycin and 100 γ of Dihydrostreptomycin per ml. by Some Strains of M. Ranae Completely Resistant to Both Antibiotics

STRAINS	PLAIN ASPARAGINE	DIHYDROSTREPTOMYCIN 100 γ PER ML.	NEOMYCIN 100 UNITS PER ML.	DIHYDROSTREPTOMYCIN 100 γ AND NEOMYCIN 100 UNITS PER ML.
Sensitive	209	0	0	0
Mr/N4fSfA	379	296	272	309
Mr/N4fSfB	581	479	419	476
Mr/N4cSfA	324	307	281	297
Mr/N4cSfB	211	167	204	201
Mr/N4cSfA	214	197	207	201
Mr/N4cSfB	224	220	183	197

Strains Fully Resistant to Both Antibiotics

If fully neomycin-resistant strains are plated in media containing 100 γ of dihydrostreptomycin, a few surviving colonies will be obtained from a large inoculum. These survivors are completely resistant to a combination of 100 units of neomycin and 100 γ of dihydrostreptomycin. The result of inoculating 0.1 ml. of 10^{-6} dilution of different stock cultures into asparagine glycerol agar containing in each ml. either 100 units of neomycin, 100 γ of dihydrostreptomycin, or the combination of both drugs in the same concentration is shown in table 1. The inoculated cells were originally grown in nutrient broth containing 0.1 per cent Triton A-20.

Mutation Rate

Mutation may be defined as a sudden heritable discontinuous change in the properties of an organism. Studies on all forms of life, including bacteria, indicate that these discontinuous heritable changes occur with a determinable prob-

ability. For example, if a *small* amount of culture medium is inoculated with a few streptomycin-sensitive cells, the chance of finding a resistant mutant in the saturated population may be negligible. On the other hand, if a *large* amount of culture medium is inoculated with the same few streptomycin-sensitive bacteria, there is a virtual certainty that streptomycin-resistant cells will be found in the saturated population. The difference lies in the fact that every time a bacterium divides there is a slight but fixed probability that a mutation will occur. It follows that, where more medium is present and more bacteria are dividing, the chance for mutation is greater. The important factor is not the amount of medium but its consequence, the size of the bacterial population. The greater genetic diversity of large bacterial populations is often responsible for effects that have been erroneously ascribed to the influence of inoculum size per se.

From these statements it may be deduced that, since small amounts of medium inoculated with sensitive cells will almost never contain certain mutants when grown, it should be possible to adjust the amount of medium upwards to the point where these mutants may be found in only a certain percentage of a series of independent cultures. The information so obtained will give a quantitative definition of mutation rate as the probability of occurrence of a mutation per bacterium per bacterial generation.

In the calculation of mutation rate in these studies, two alternative formulas proposed by Luria and Delbruck (10) have been employed. As described, the first formula is based on the percentage (P_0) of a series of independent cultures which when fully grown from a small nonmutant inoculum do not contain any mutant (resistant) cells:

$$a = -\frac{1.6}{N}\log_{10} P_0 = -\frac{\ln 2}{N}\ln P_0$$

where "a" is the mutation rate and N is the mean number of bacteria per culture. The second method for estimating mutation rate (a) is based on the average number of mutants (r) per culture. The formula correlating the number of mutants with mutation rate is:

$$r = 1.6\,aN\log_{10}\frac{CaN}{0.693} = \frac{aN}{\ln 2}\cdot\frac{\ln CaN}{\ln 2}$$

In this formula, C is the number of independent cultures. The use of the second formula depends on the assumption that mutant cells divide at the same rate as normal cells, a premise often unsubstantiated and obviously in error in the case of streptomycin-dependent cells.

It should be emphasized that all of the independent cultures are grown in the complete absence of the antibiotic and then after full growth are plated in streptomycin merely as a selective method of determining their genetic composition. That mutation to resistance occurs spontaneously in the absence of the antibiotic has been observed by Demerec (3), using the methods derived by Luria and Delbruck and related to the earlier studies of variation in independent cultures by Parr and Robbins (11).

In the determination of mutation rates to complete streptomycin resistance, approximately 300 to 600 cells of *M. ranae* were incubated in 2.0 ml. or 0.2 ml. of sterile Triton A-20 nutrient broth contained in each of numerous small tubes or 1 ml. pipettes, respectively. Precautions were taken to prevent evaporation. The culture used for inoculation was always tested independently in 25 γ of dihydrostreptomycin agar to be certain that there was virtually no probability of inoculating a resistant cell into a culture. No visible colonies were ever found in the test plates.

TABLE 2

Mutation Rate to Complete Dihydrostreptomycin Resistance for Various Strains of M. Ranae

STRAIN	NUMBER OF CULTURES	AVERAGE NUMBER OF BACTERIA PER CULTURE	PER CENT OF CULTURES WITHOUT MUTANTS	NUMBER OF MUTANTS PER CULTURE		MUTATION RATE	
				average	range	from P_0	from r
	C	N	P_0	r			
Sensitive	50	11×10^8	50	2.72	0–21	0.43×10^{-9}	0.49×10^{-9}
Sensitive	200	3×10^8	60	1.91	0–114	1.2×10^{-9}	0.94×10^{-9}
Sensitive	50	5.5×10^8	42	3.10	0–56	1.1×10^{-9}	1.1×10^{-9}
Sensitive	110	5×10^8	70	0.54	0–8	0.5×10^{-9}	0.3×10^{-9}
Mr/N1	50	5×10^8	46	3.06	0–50	1.1×10^{-9}	1.1×10^{-9}
Mr/N3	50	7.8×10^8	46	3.60	0–36	0.69×10^{-9}	0.96×10^{-9}
Mr/N4	50	4.1×10^8	22	7.22	0–187	2.6×10^{-9}	2.8×10^{-9}
Mr/Sla	200	4.9×10^8	3	20.50	0–250	4.6×10^{-9}	4.7×10^{-9}
Mr/Sld	50	6.4×10^8	4	20.04	0–511	3.5×10^{-9}	4.3×10^{-9}
Mr/Slf	62	1.5×10^8	3.2	19.92	0–390	1.6×10^{-8}	17×10^{-9}
Mr/Slg	50	2.2×10^8	—	257.0	73–375	—	110×10^{-9}

Sensitive = Original wild-type strain of *M. ranae*.
Mr/N1 = Neomycin-resistant strain of first-step selection.
Mr/N3 = Neomycin-resistant strain of second-step selection.
Mr/N4 = Neomycin-resistant strain of fourth-step selection.
Mr/Sla and Mr/Sld are slightly dihydrostreptomycin-resistant strains.
Mr/Slf and Mr/Slg are intermediate dihydrostreptomycin-resistant strains.

After establishment of the small independent cultures by aliquots from a large parent culture, the bacteria were incubated at 37°C. for four days, yielding a titer of about 10^8 cells per ml. The average number of bacteria per saturated culture was determined by assaying ten independent tubes and obtaining a representative figure. In fully grown cultures the variation in titer from one specimen to another is not very great.

After growth was complete, each whole culture of 2 ml. in a small tube or 0.2 ml. in a pipette was poured or expelled into a Petri dish and mixed thoroughly with approximately 15 ml. of asparagine glycerol agar (45°C.) containing 25 γ of dihydrostreptomycin per ml. After five days' incubation at 37°C., the visible colonies were counted. Where an exceptional culture was found to contain a

TABLE 3

Stability of Neomycin-resistant Mutants

Number of Colonies Developed on Various Concentrations of Neomycin

CONCENTRATION OF NEOMYCIN (UNIT PER ML.)	FIFTH SUBCULTURE INOCULUM (0.1 ML. OF THE INDICATED DILUTION)				TENTH SUBCULTURE INOCULUM (0.1 ML. OF THE INDICATED DILUTION)			
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Strain Mr/N1								
0				433 427				295 339
0.5			*	402				186
			*	426				220
1.0		*	294			*	164	
		*	247			*	127	
2.5	0	0			0	0		
	0	0			0	0		
Strain Mr/N2								
0				335				164
				303				164
2.5		127	0			55	0	
		109	0			43	0	
5.0	0				0			
	0				0			
6.0	0				0			
	0				0			
Strain Mr/N3								
0				341				130
				369				142
2.5		*	488			3,350	45	
		*	518			4,320	29	
5.0	2,310	38			2,310	41		
	2,250	30			2,980	42		
100	1,710	21			1,880	28		
	2,150	28			2,380	26		
Strain Mr/N4								
0				355				126
				302				113
100				273				64
				277				80

* Too numerous for counting.

Mr/N1 = Neomycin-resistant strain of first-step selection.

Mr/N2 = Neomycin-resistant strain of second-step selection.

Mr/N3 = Neomycin-resistant strain of third-step selection.

Mr/N4 = Neomycin-resistant strain of fourth-step selection.

TABLE 4

Stability of Dihydrostreptomycin and Cross-resistant Mutants

Number of Colonies Developed on Various Concentrations of Dihydrostreptomycin

CONCENTRATION OF DIHYDROSTREPTOMYCIN (γ PER ML.)	FIFTH SUBCULTURE INOCULUM (0.1 ML. OF THE INDICATED DILUTION)				TENTH SUBCULTURE INOCULUM (0.1 ML. OF THE INDICATED DILUTION)			
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Strain Mr/Sld								
0				145				92
				182				89
1			*	165			*	99
			*	95			*	74
10	2,930	29			2,500	18		
	2,740	27			2,240	21		
100	13	0			2	0		
	17	0			1	0		
Strain Mr/Slf								
0				115				44
				117				46
1				111				46
				109				39
10			5,870	52			3,750	
			7,650	85			3,980	
100	735	7			126			
	756	6			161			
Strain Mr/Sf								
0			242					35
			267					45
100			234					29
			268					42
Strain Mr/N, S								
0			154					101
			181					115
**100			153					134
			145					128

* Too numerous for counting.

** 100 units of neomycin per ml. Asparagine was also incorporated.

Mr/Sf = complete dihydrostreptomycin-resistant strain of *M. ranae*.

Mr/N, S = complete neomycin-dihydrostreptomycin—resistant strain of *M. ranae*.

Mr/Sld = slightly dihydrostreptomycin-resistant strain.

Mr/Slf = intermediate dihydrostreptomycin-resistant strain.

large number of resistant cells it is most probable that the mutant individual cells represented a clone, that is, the descendants of a single early mutation. The small number of mutants actually detected render such an event the exception rather than the rule.

The mutation rate of the original wild-type *M. ranae* to complete streptomycin resistance is found to be about 10^{-9}. This means that by the time a sensitive population has grown to one thousand million bacteria it may be anticipated that some accident in the reproduction of one of these cells will result in the "spontaneous" origin of a new resistant type, with the qualification that wide random variations dependent on probability may be expected to occur in either direction. We must deal with an average value which in an independent experiment tends only to be approached. Yet when sufficient independent cultures are used the average value is reasonably reproducible as may be seen in table 2. The neomycin-resistant strains of various levels showed a mutation rate to complete streptomycin resistance similar to the rate found for the sensitive wild-type *M. ranae* stock. It should be noted, however, that the mutation rate of strains of *M. ranae* showing a low grade of resistance to dihydrostreptomycin was approximately five times as high as the basic rate for sensitive bacteria, and that of the intermediate mutants was ten to one hundred times greater. A quantitative summary of the information concerning mutation to dihydrostreptomycin resistance (25 γ per ml.) for various strains of *M. ranae* is given in table 2. The mutation rate for streptomycin resistance in *E. coli* is about 1×10^{-10} (12), and for *Hemophilus influenzae* it is approximately 4×10^{-9} (13).

Stability of Mutants

The properties of resistance to neomycin and dihydrostreptomycin possessed to various degrees by the mutant stocks derived in these experiments are transmissible through subculture in the absence of the selective agent for at least ten transfers with little or no change. A comparison of resistance properties after five and ten transfers in plain nutrient broth containing 0.1 per cent Triton A-20 is given in tables 3 and 4.

DISCUSSION

It is only by the ability to maintain resistance in the absence of a selective antibiotic that the stocks isolated in the course of these experiments can be properly designated as mutant. They are thereby set apart from strains of cells physiologically adjusted to particular substrates through the increased elaboration of adaptive enzyme systems. Some confusion has arisen in the literature because strains of cells described as mutants have been found to revert more or less rapidly to normal on periodic subculture or prolonged storage. Excluding enzymatic adaptation, this dilemma is resolved by the realization that mutation is a two-way process. With the exception of complex chromosomal rearrangements as yet undemonstrated in bacteria, there is always the possibility that a genic change will undergo reverse mutation to give the original phenotype. Such reverse mutation allows the development of a few nondependent streptomycin-resistant colonies when large numbers of streptomycin-dependent cells are plated

in the absence of streptomycin (12). Usually the reverse mutation restores to the cell its original properties, including a rate of growth more rapid than the majority of mutants in a normal environment (otherwise the mutant cells might have become the "normal" type in the evolutionary pressures of natural selection). Reverse mutation therefore provides a mechanism for the qualitative change of population components under the slow dynamic population changes of refrigerated cultures or the more rapid changes possible by subculture.

If corroborated with human pathogens, the relatively greater mutation rate of strains possessing intermediate dihydrostreptomycin resistance to full resistance may be of clinical significance. Yegian and Vanderlinde report that the response of *M. ranae* to streptomycin is very similar to that of human varieties of *Mycobacteria* (14). The use of low doses of dihydrostreptomycin then would be seen as a potential hazard, since the mutants unable to survive at high concentrations would provide the potential progenitors of a rapidly developing population of highly resistant cells. Adequate levels of dihydrostreptomycin of multiple chemotherapy should postpone such an occurrence. The same conclusions should apply to streptomycin as apply to the dihydro form.

A most interesting aspect of mutation to resistance remains obscure. What is the relation between mutation and the biochemical basis for resistance? Almost nothing is known about the physiological nature of neomycin action, and investigators must be prepared for the possibility that neomycin, in its present impure state, is a complex of antibiotic entities. A tentative biochemical interpretation of streptomycin resistance in *Escherichia coli* has been advanced by Smith, Oginsky, and Umbreit (15). These workers believe that streptomycin may act by inhibiting the condensation of oxalacetate and pyruvate in a phase of the terminal respiration system. Resistant strains have possibly developed an alternative method of producing some substance essential to metabolism and ordinarily derived by the oxalacetate-pyruvate condensation. The dependent strain is assumed to drive the essential building block directly from streptomycin. The terminal respiratory cycle, uncertain as it is for *Escherichia coli*, is even more obscure and very probably different in the *Mycobacteria*.

Genetic tests with the recombining strain of *E. coli* show that independently originating mutations to full streptomycin resistance or dependence (25 γ per ml.) are, in the majority of cases, allelic; that is, occupy the same or a common spatial position in the heredity material (16). Mutations in *E. coli* to slight streptomycin resistance are considered by Demerec to be due to a separate system of small mutations.

The accumulation of small relatively frequent mutations as an alternative method of acquiring full streptomycin resistance provides a hypothetical interpretation to the more rapid mutation rate of intermediate resistant strains. If full resistance can be obtained in a facultative multiple-step system by either a single large mutation (in the phenotypic sense) or by a series of small mutations, it would explain why cells of intermediate resistance that have already accumulated several small mutations would more readily attain the residual number necessary for full resistance and the complete by-passing of a metabolic reaction blocked by streptomycin.

At the same time this interpretation, if substantiated, points up a very real weakness of bacterial genetics in its present state of development. Unless mutations in *Mycobacteria* can be located in linkage groups of genes with the precision of classical genetic methods, a number of independent mutation systems leading to the same phenotypic effect may be experimentally inseparable. Until this problem is solved, the bacterial geneticist must present a determination of "mutation rates" in *M. ranae* to streptomycin resistance with the qualification that a number of epigenetically independent but physiologically interactive mutations may be disguised as a single system.

SUMMARY

Mutations to neomycin in *Mycobacterium ranae* occur by way of an obligatory multiple-step pattern. Complete resistance is not obtainable unless cells are subcultured in gradually increasing levels of the antibiotic. By this method, stocks resistant to 200 units of neomycin per ml. of asparagine glycerol agar have been obtained.

Mutations to dihydrostreptomycin resistance in *M. ranae* occur by way of a facultative multiple-step pattern. The bacteria may become completely resistant to 25 γ of dihydrostreptomycin per ml. of asparagine glycerol agar in one step, or may proceed to complete resistance through transitional grades of intermediate resistance.

The combined effect of dihydrostreptomycin and neomycin is shown to be additive rather than synergistic. Strains resistant to the combined antibiotics may be obtained by exposing a neomycin-resistant stock to dihydrostreptomycin and selecting survivors. Cross resistance is either absent or of minor magnitude.

In a series of independent experiments the rate of mutation from sensitivity to full dihydrostreptomycin resistance was found to be approximately 10^{-9} as calculated by one of alternative methods. Strains of low and intermediate streptomycin resistance have rates to full resistance from five to one hundred times as high as the sensitive strain.

It is postulated that the determination of a mutation rate in bacteria may represent in specific instances a calculation based on multiple mutations in several experimentally indistinguishable genetic systems.

SUMARIO

Estudios Genéticos sobre la Producción de Resistencia a la Neomicina y la Dihidroestreptomicina en el Mycobacterium ranae

Las mutaciones a la neomicina en el *Mycobacterium ranae* sobrevienen conforme a un patrón obligatorio de muchos tiempos. No cabe obtener resistencia total a menos que se subcultiven las células en concentraciones cada vez mayores del antibiótico. Con este método se han obtenido razas resistentes a 200 unidades de neomicina por ml. de agar-glicerol-asparagina.

Las mutaciones de la resistencia a la dihidroestreptomicina en el *M. ranae* sobrevienen conforme a un patrón facultativo de muchos tiempos. Las bacterias

pueden volverse totalmente resistentes a 25 unidades de dihidroestreptomicina por ml. de agar-glicerol-asparagina en un tiempo o proseguir hasta la resistencia total a través de grados transicionales de resistencia intermedia.

El efecto combinado de la dihidroestreptomicina y la neomicina se mostró aditivo más bien que sinérgico. Pueden obtenerse cepas resistentes a los antibióticos combinados exponiendo una raza neomicinorresistente a la dihidroestreptomicina y escogiendo los microbios sobrevivientes. La resistencia cruzada o bien no existe o es de poca magnitud.

En una serie de experimentos independientes, y calculado con una de dos técnicas alternativas, el coeficiente de mutación de sensibilidad a plena resistencia a la dihidroestreptomicina resultó ser aproximadamente 10^{-9}. Las cepas dotadas de estreptomicinorresistencia baja e intermedia muestran coeficientes hasta la plena resistencia de cinco a cien veces mayores que las cepas sensibles.

Postúlase que la determinación del coeficiente de mutación en las bacterias puede representar en casos específicos un cálculo basado en mutaciones múltiples en varios sistemas genéticos experimentalmente indistinguibles.

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EFFECT OF NEOMYCIN ON THE TUBERCLE BACILLUS AND IN EXPERIMENTAL TUBERCULOSIS OF GUINEA PIGS[1,2,3]

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INTRODUCTION

The *in vitro* inhibition of growth of tubercle bacilli by neomycin was first reported by Waksman (1, 2, 3), and these studies have been extended by Hobby (4) and by Rake (5) to include the effect of this antibiotic upon a tuberculous infection in mice. In this report we shall discuss the activity of neomycin upon the growth of tubercle bacilli (strain H37Rv) in three different liquid media, the production of neomycin-resistant H37Rv strains, and the effect of neomycin upon experimentally induced tuberculosis in guinea pigs produced by streptomycin- and neomycin-sensitive and -resistant strains.

IN VITRO ACTIVITY OF NEOMYCIN

In January 1949 Doctor Waksman kindly supplied us with a small quantity of neomycin[4] to enable us to study its activity against streptomycin-sensitive and -resistant microorganisms. Three types of liquid media were employed: the Tween-albumin medium of Dubos; Proskauer and Beck's synthetic medium; and Proskauer and Beck's medium with 10 per cent beef serum. The test cultures were carried in Tween-albumin medium, and the inoculum into each tube was 0.1 cc. of a 10- to 12-day culture. The results are recorded in table 1.

It will be noted that 0.13 to 0.52 units of neomycin per cc. of medium produced inhibition of growth for 14 days in all three media. The streptomycin-resistant microorganisms were inhibited to the same degree as the streptomycin-sensitive ones. The activity of neomycin was only slightly diminished in the presence of serum. These results were later confirmed with another sample of neomycin[5]. When tested in a similar fashion, using the same three types of liquid media, it was found that 0.31 to 0.62 units per cc. was the minimal inhibitory concentration for the H37Rv microorganisms, both sensitive and resistant to streptomycin.

PRODUCTION OF NEOMYCIN-RESISTANT MICROORGANISMS

A strain of neomycin-resistant H37Rv microorganisms was produced by serial transfer in Tween-albumin liquid medium containing increased concentrations

[1] From the Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

[2] This study was supported (in part) by a research grant from the National Institutes of Health, Public Health Service.

[3] A preliminary report of this work was presented at the Eighth Streptomycin Conference of the Veterans Administration, Atlanta, Georgia, November 1949.

[4] Original neomycin lot 6C, potency 52 units per mg., was obtained from Dr. Selman A. Waksman.

[5] Neomycin sulfate, lot 116, 180 units per mg., was kindly supplied by Pfizer and Co. through the courtesy of Doctors Hobby and Patelski.

of neomycin (Pfizer, lot 116). For each transfer, 0.1 to 0.2 cc. of the contents of the tube with the highest concentration of neomycin showing good growth after 12 to 18 days of incubation was seeded into each of a fresh series of tubes of liquid medium containing neomycin. In this manner, resistance to 1,000 units of neomycin per cc. was evidenced after seven transfers. Little increase in

TABLE 1

*In Vitro Effect of Neomycin**

TEST CULTURE	MEDIUM	CONCENTRATION IN UNITS PER CC.	GROWTH IN DAYS			
			4	8	14	21
H37Rv Streptomycin-sensitive	Tween-albumin liquid	0	1+	3+	4+	4+
		0.03	1+	2+	4+	4+
		0.065	0	1+	3+	4+
		0.13	0	0	±	3+
		0.26	0	0	0	±
		0.52	0	0	0	±
	Proskauer and Beck's synthetic	0	±	2+	3+	4+
		0.03	0	1+	3+	3½
		0.065	0	1+	3+	3½
		0.13	0	0	0	0
		0.26	0	0	0	0
		0.52	0	0	0	0
	Proskauer and Beck's with 10 per cent beef serum	0	1+	2+	4+	4+
		0.03	1+	2+	3½	4+
		0.065	1+	2+	3½	4+
		0.13	±	1+	2½	3+
		0.26	0	±	2+	3+
		0.52	0	0	0	1+
H37Rv Streptomycin-resistant	Tween-albumin liquid	0	1+	3+	4+	4+
		0.03	1+	2+	3½	4+
		0.065	1+	2+	3+	3½
		0.13	±	1+	2+	3+
		0.26	0	±	±	1½
		0.52	0	0	0	0

* Waksman, lot 6C, 52 units per mg.

resistance was manifested until the fourth transfer, but succeeding series thereafter showed rapid rise in resistance.

A simultaneous and comparable series of transfers of the same original culture in medium containing streptomycin produced a culture resistant to 1,000 γ of streptomycin per cc. after six transfers.

Resistance to neomycin remained the same after bimonthly transfers in neomycin-free medium for seven months. The H37Rv microorganisms made resistant to neomycin, as described above, were also found to be resistant to 1,000 units per cc. of Upjohn neomycin sulfate[6].

[6] Lot 9084, 200 units per mg., was kindly supplied by Dr. H. F. Hailman, Upjohn Company, Kalamazoo, Michigan.

EFFECT OF NEOMYCIN ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS

Eighty guinea pigs weighing between 400 and 500 gm. were infected subcutaneously in the inguinal region with H37Rv microorganisms. Of the 80 animals, 30 (Group I) were infected with H37Rv microorganisms (0.15 mg. dry weight) sensitive to both streptomycin and neomycin, 30 (Group II) with the

TABLE 2

Effect of 48 Days of Neomycin Treatment on Experimental Tuberculosis in Guinea Pigs

TREATMENT AND DOSAGE	INFECTING ORGANISM	INFECTING DOSE (SUBCUTANEOUS)	DAYS OF INFECTION	DAYS OF TREATMENT	NUMBER SURVIVING 60 DAYS	DEGREE OF TUBERCULOSIS*				
						Lungs	Liver	Spleen	Lymph Nodes	Total
0 (Controls)	H37Rv	0.15 mg.	60	0	10/10	1.8	2.3	2.8	3.0	10
Neomycin** 5,000 units intramuscularly once a day	H37Rv	0.15 mg.	60	48	10/10	0.4	1.3	1.4	1.5	4.6
Streptomycin 10 mg. intramuscularly once a day	H37Rv	0.15 mg.	60	48	9/9	0.1	0	0.1	1.2	1.4
0 (Controls)	H37Rv neomycin-resistant	0.16 mg.	60	0	10/10	1.9	2.3	2.0	3.1	9.2
Neomycin 5,000 units intramuscularly once a day	H37Rv neomycin-resistant	0.16 mg.	60	48	10/10	1.6	2.5	2.0	3.0	9.1
Streptomycin 10 mg. intramuscularly once a day	H37Rv neomycin-resistant	0.16 mg.	60	48	10/10	0.4	0	0.15	1.6	2.2
0 (Controls)	H37Rv streptomycin-resistant	0.2 mg.	60	0	9/10	1.9	2.5	2.9	3.6	11
Neomycin 5,000 units intramuscularly once a day	H37Rv streptomycin-resistant	0.2 mg.	60	48	10/10	0.2	0.8	0.5	1.8	3.3

* Degree of tuberculosis is based on a maximum of 16 for each animal (4 each for the lungs, liver, spleen, and lymph nodes, according to the amount of gross tuberculous disease in these organs).

** Pfizer neomycin sulfate, lot 116, 180 units per mg., and lot 179, 200 units per mg.

H37Rv neomycin-resistant microorganisms (0.16 mg. dry weight), and 20 (Group III) with H37Rv microorganisms (0.2 mg. dry weight) that were highly resistant to streptomycin. In each of the first two groups, 10 animals were treated with neomycin, 10 with streptomycin, and 10 remained untreated. In the last group, 10 received neomycin, and 10 remained untreated. Treatment was begun 12

days after infection, at which time all animals elicited a positive skin reaction when tested intracutaneously with 5 per cent Old Tuberculin. Sixty days after infection, animals in each group were sacrificed as follows:

Group I (infected with H37Rv streptomycin- and neomycin-sensitive microorganisms): One-half of the controls, one-half of those treated with neomycin, and one-half treated with streptomycin were killed. The other half were held for further treatment and observation.

Group II (infected with H37Rv neomycin-resistant microorganisms): All of the animals in this group were killed, as it was obvious that neomycin was not affecting the course of the disease and that streptomycin was exerting its usual beneficial effect.

TABLE 3

Effect of Prolonged Treatment with Neomycin on Experimental Tuberculosis in Guinea Pigs

TREATMENT AND DOSAGE	INFECTING ORGANISM	DAYS OF INFECTION	DAYS OF TREATMENT	NUMBER SURVIVING 129 DAYS PER NUMBER LIVING AT END OF 60 DAYS	DEGREE OF TUBERCULOSIS				
					Lungs	Liver	Spleen	Lymph Nodes	Total
0 (Controls)	H37Rv	129	0	0/5*	2.8	3.6	3.9	3.5	13.6
Neomycin—5,000 units once daily for 48 days; rest period for 20 days; 10,000 units once daily for 49 days	H37Rv	129	97	4/5**	0.9	1.6	1.5	2.1	6.1
Streptomycin—10 mg. once daily	H37Rv	129	97	4/4	0.25	0.1	0.1	0.9	1.4
0 (Controls)	H37Rv Streptomycin-resistant	129	0	2/4†	2.7	3.0	3.0	3.5	12.2
Neomycin—5,000 units once daily for 48 days; rest period for 20 days; 10,000 units once daily 49 days	H37Rv Streptomycin-resistant	129	97	5/5	0.5	0.6	0.4	1.2	2.7

* All died of tuberculosis.

** One died evidently of drug toxicity.

† One died of pneumonia; one of tuberculosis.

Group III (infected with H37Rv streptomycin-resistant microorganisms): One-half of the control animals and one-half of the animals treated with neomycin were killed. The remaining animals were held for further treatment and observation. The relative amount of gross tuberculous disease found at autopsy in these guinea pigs is presented in table 2.

After a lapse of 20 days, during which time neomycin and streptomycin were discontinued in the remaining treated guinea pigs of groups I and III, treatment was again instituted. Neomycin was now given in twice the previous amount (10,000 units intramuscularly once a day of neomycin hydrochloride[7]), and

[7] Pfizer, lot 190, 225 units per mg.

streptomycin was continued in the same dosage (10 mg. intramuscularly once a day). After an additional 49 days of treatment, all surviving animals were sacrificed. The results are recorded in table 3.

From the results recorded in tables 2 and 3 it may be concluded that these preparations of neomycin produced a definite retarding action on tuberculosis in guinea pigs infected with streptomycin-sensitive as well as streptomycin-resistant H37Rv microorganisms, when given in dosage of 5,000 units intramuscularly once daily for 48 days. This beneficial effect of neomycin was slightly, but definitely, inferior to that of streptomycin, 10 mg., intramuscularly once daily, in those animals infected with streptomycin-sensitive organisms.

An additional seven weeks of treatment with a dosage of 10,000 units of neomycin once daily produced no further beneficial effect on the disease; those animals which had been infected with the streptomycin-sensitive microorganisms showed slightly more disease than their group mates which had been killed after 48 days of therapy. Those animals infected with the streptomycin-resistant microorganisms showed approximately the same degree of tuberculosis as did their group mates killed after 48 days of therapy.

Neomycin had no effect on the tuberculosis produced by the neomycin-resistant H37Rv microorganisms, whereas streptomycin demonstrated an excellent retarding action on this disease.

TOXICITY

The preparations of neomycin used in this experiment produced a definite toxic effect on the animals, which was manifested by progressive weight loss. This was more noticeable in the guinea pigs receiving 10,000 units than in those receiving 5,000 units a day.

SUMMARY AND CONCLUSIONS

Neomycin produced inhibition of growth of H37Rv microorganisms in a concentration of 0.3 to 0.6 units per cc. of liquid medium. The presence of Tween 80 (in the Tween-albumin medium of Dubos) did not appreciably alter the minimal inhibitory concentration of the drug. The activity of neomycin was only slightly diminished in the presence of 10 per cent beef serum.

A neomycin-resistant strain of H37Rv was produced by serial transfer in Tween-albumin liquid medium containing increasing concentrations of the drug. After seven transfers, the microorganisms grew readily in 1,000 units of neomycin per cc. In a simultaneous and comparable series of transfers in streptomycin-containing medium, the same strain of *M. tuberculosis* manifested resistance to 1,000 γ of streptomycin per cc. after six transfers. Resistance to neomycin has not diminished after seven months of transfers in neomycin-free medium.

The preparations of neomycin used in this experiment exerted a marked beneficial action on tuberculous disease in guinea pigs infected with streptomycin-sensitive and streptomycin-resistant H37Rv microorganisms. Neomycin in dos-

age of 5,000 units once daily, however, was slightly less effective than streptomycin, 10 mg. once daily, when given for 48 days to animals infected with the streptomycin-sensitive strain. After an additional treatment period of 49 days, during which 10,000 units of neomycin and 10 mg. of streptomycin, respectively, were given daily, those animals treated with streptomycin still showed slightly less disease than those treated with neomycin.

Therapy with neomycin was ineffective for guinea pigs infected with a neomycin-resistant strain of the H37Rv microorganisms, whereas streptomycin exerted its usual beneficial action.

Neomycin in dosage of 5,000 or 10,000 units, intramuscularly, once daily, produced progressive weight loss in the guinea pigs.

SUMARIO Y CONCLUSIONES

Efecto de la Neomicina sobre el Bacilo Tuberculoso

La neomicina produjo inhibición del desarrollo de los microbios H37Rv a una concentración de 0.3 a 0.6 unidades por cc. de medio líquido. La presencia de Tween 80 (en el medio de Tween-albúmina de Dubos) no afectó apreciablemente la mínima concentración inhibidora de la droga. La actividad de la neomicina apenas disminuyó en presencia de 10 por ciento de suero de bovino.

Se produjo una cepa neomicinorresistente de H37Rv mediante una serie de pases por el medio líquido de Tween-albúmina con concentraciones crecientes de la droga. Al cabo de siete pases, los microbios ya podían crecer sin dificultad en 1,000 unidades de neomicina por cc. En una serie simultánea y comparable de pases por un medio que contenía estreptomicina, la misma cepa del *M. tuberculosis* manifestó resistencia a 1,000 γ de estreptomicina por cc. al cabo de seis pases. La resistencia a la neomicina no ha disminuído a los siete meses de pases por un medio sin neomicina.

Las preparaciones de neomicina utilizadas en este experimento ejercieron decidido efecto beneficioso sobre la enfermedad tuberculosa en cobayos infectados com microbios H37Rv tanto sensibles cuanto resistentes a la estreptomicina. Sin embargo, la neomicina, a dosis de 5,000 unidades una vez al día, se mostró ligeramente menos eficaz que la estreptomicina, 10,000 γ una vez diaria, cuando se administró durante 48 días a animales infectados con la cepa estreptomicinosensible. Tras otro período de 49 días de tratamiento, durante el cual se administraron a diario, 10,000 unidades de neomicina y 10,000 γ de estreptomicina respectivamente, los animales tratados con estreptomicina revelaban todavía ligeramente menos enfermedad que los tratados con neomicina.

La terapéutica con neomicina resultó ineficaz para los cobayos infectados con una cepa neomicinorresistente del microbio H37Rv, en tanto que la estreptomicina ejerció en ellos su habitual efecto beneficioso.

La neomicina, a dosis de 5,000 ó 10,000 unidades, intramuscularmente, una vez diaria, produjo pérdida gradual de peso en los cobayos.

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ELECTROCARDIOGRAMS WITH PROMINENT S WAVES IN ALL STANDARD LIMB LEADS[1]

Associated Patterns in Multiple Precordial Leads

WILLIAM WEISS

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INTRODUCTION

Electrocardiograms in which the QRS complexes are predominantly negative due to deep S waves in all three standard limb leads are rare. They have been described by several authors in the past (1, 2, 3, 4, 6, 7, 10, 11, 13, and 14), but little or no correlation has been made with associated patterns in the multiple precordial leads. It is the purpose of this paper to present an analysis of 6 cases in which this electrocardiographic pattern was observed, to correlate the pattern of the precordial leads available in 2 of these cases, and to discuss the significance of this unusual limb-lead pattern as found in patients with pulmonary tuberculosis.

CASE MATERIAL

Approximately 2,850 electrocardiograms have been made at the Olive View Sanatorium in the past thirteen years. A search of these tracings disclosed 6 cases in which the QRS complexes were predominantly negative, due to the presence of deep S waves in all limb leads. Included are tracings which showed an equiphasic QRS complex in lead III because of the variation in amplitude that may occur in this lead with respiration. Tracings with prolonged QRS duration were excluded.

In table 1 are presented some of the pertinent clinical data on these patients. As may be seen, 4 of the 6 patients had some chest deformity. One (Case 4) had a congenital anomaly, funnel chest; and 3 patients had had thoracoplasty for the treatment of pulmonary tuberculosis. Of particular interest was the roentgenographic appearance of the heart. In all 6 patients the heart appeared to be vertical in position. In none was there notable shift of the mediastinum or any peculiarity of cardiac silhouette. In some cases, however, there was slight prominence of the pulmonary conus as viewed in the posteroanterior roentgenograph of the chest, suggesting a clockwise rotation of the heart on its longitudinal axis, i.e., viewing the heart from the apex toward the base.

The clinical diagnoses in all cases included far advanced pulmonary tuberculosis. Two patients (Cases 1 and 5) were thought to have myocardial infarction which was not substantiated at necropsy. Instead, cardiac failure was found to be due to chronic cor pulmonale. Three other patients (Cases 2, 3, and 6) had been subjected to thoracoplasty on the right, and one case had a funnel chest. The latter had repeated electrocardiograms over a period of fifteen years before she died, and all tracings showed the same pattern in the limb leads.

[1] From Olive View Sanatorium, Olive View, California.

All but one of the patients were dead at the time of this investigation. Two died of cor pulmonale. Three were discharged from the hospital and died from four to nine years later, and information on the causes of death was not available. Case 6 is still under observation following pneumonectomy.

TABLE 1

Analysis of Patients Showing Prominent S Waves in all Standard Limb Leads of the Electrocardiogram

PATIENT NUMBER	AGE	SEX	CLINICAL DIAGNOSIS	FOLLOW-UP	POST-MORTEM DIAGNOSIS
1	29	M	Far advanced pulmonary tuberculosis, myocardial infarct, congestive failure	Died under observation	Pulmonary tuberculosis, emphysema, chronic cor pulmonale
2	36	M	Far advanced pulmonary tuberculosis, right thoracoplasty (3 ribs)	Died 4 years later	
3	36	M	Far advanced pulmonary tuberculosis, right thoracoplasty (7 ribs)	Died 4 years later	
4	34	F	Far advanced pulmonary tuberculosis, funnel chest	Died 9 years later	
5	57	M	Far advanced pulmonary tuberculosis, emphysema, myocardial infarct, congestive failure	Died under observation	Pulmonary tuberculosis, emphysema, chronic cor pulmonale
6	29	M	Far advanced pulmonary tuberculosis, right thoracoplasty (10 ribs)	Still under observation	

In summary, right ventricular enlargement (chronic cor pulmonale) or a chest deformity (congenital or artificial) was present in all 6 cases.

ELECTROCARDIOGRAMS

In addition to the standard limb leads, a single precordial lead, IVF, was available in 3 cases and multiple precordial leads, in 2 cases.[2] Alpha QRS ranged from

[2] Definitions for the various leads are as follows:
Leads 1, 2, and 3 (or I, II, and III): standard limb leads
Lead IVF: Chest lead with the exploring electrode over the cardiac apex and the indifferent electrode on the left leg

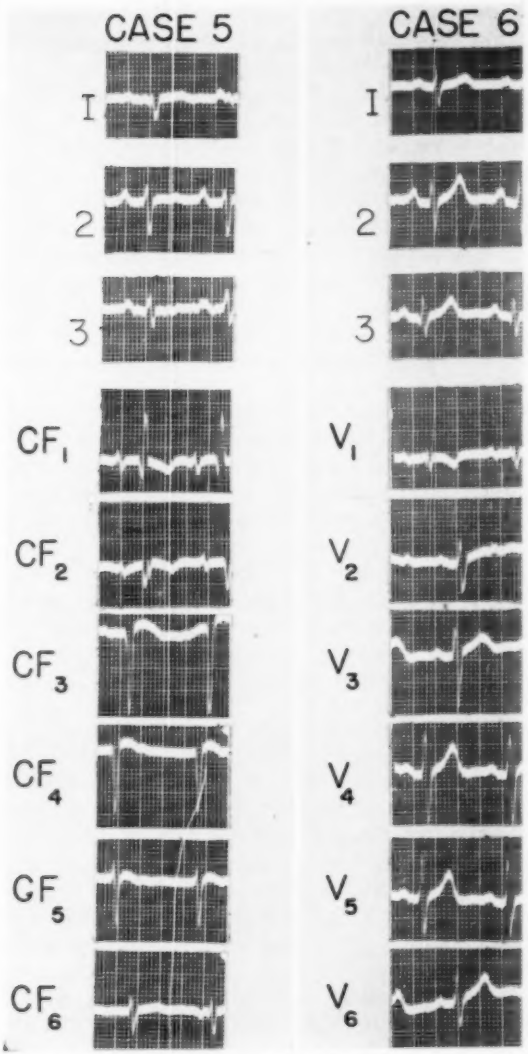

FIG. 1. Electrocardiograms in Cases 5 and 6 (see text)

Lead CF_{1-6}: Chest leads with the exploring electrode in chest positions 1 to 6 (as defined by the American Heart Association) and the indifferent electrode on the left leg

Leads V_{1-6}: Chest leads with the exploring electrode in chest positions 1 to 6 and the indifferent electrode connected to the Wilson central terminal.

−125 to −150 degrees. All leads IVF showed QRS complexes in which the R waves were smaller than the S waves. Cases 5 and 6 were studied with multiple precordial leads and will be described in detail.

CF leads were done in Case 5 (figure 1). The P wave in CF_1 and CF_2 was diphasic with an intrinsicoid deflection. The QRS complexes showed a deep Q wave in CF_1 with a late R wave. QRS was W-shaped in CF_2 and there was a QS wave in CF_3. R waves were small and the S waves deep in the rest of the precordial leads. Therefore, the transitional zone was shifted to the left. The T waves were inverted in the first 3 precordial leads and low but upright in the last 3 leads. Roentgenogram of the chest showed an enlarged vertical heart, extensive bilateral pulmonary tuberculosis, and emphysema. There was clinical evidence of right ventricular failure and, because of the QS waves in CF_2 and CF_3, a clinical diagnosis of old anteroseptal myocardial infarction was made. Post-mortem examination revealed chronic cor pulmonale but failed to reveal myocardial infarction.

Multiple precordial leads in Case 6 were V leads (figure 1). V_1 to V_6 showed deep S waves with shift of the transitional zone to the left. T was inverted in V_1 and low but upright in V_2. Additional electrocardiographic studies in this patient included comparison of the standard limb leads with the patient in five different body positions: supine, prone, sitting, right and left decubitus. No significant changes developed. This patient had an extensive right thoracoplasty but no cardiac enlargement or signs of cardiac failure. The heart was vertical in the roentgenogram. Following a right pneumonectomy there were no changes in his electrocardiogram or the position of his heart by roentgenogram and he is still under observation.

DISCUSSION

The standard limb-lead pattern characterized by prominent S waves in all 3 leads is seen rarely. Its incidence at this institution has been 0.2 per cent, a figure comparable with previous estimates (1, 2, 4, 6, 10). In none of these reports is the associated pattern in multiple precordial leads described. Myers, Klein, and Stofer (9) mentioned 2 cases and illustrated the electrocardiogram of one with multiple precordial leads (unipolar leads). Wilson and associates (12) also illustrate such a case. In the present series of 6 cases, multiple precordial leads are available in only 2. This is unfortunate because a thorough electrocardiographic study of individuals who present this rare limb-lead pattern should help to clarify its etiology.

From a review of the literature and the present series of cases, we can classify patients showing a pattern of negative QRS complexes due to deep S waves in all standard limb leads as follows: (*1*) those with normal hearts in the presence of some extracardiac factor which may influence the position of the heart within the thorax; and (*2*) those with right ventricular enlargement.

Goldberger and Schwartz (5) state that this pattern may occur in normal subjects, but the material which these authors presented is composed of abnormal subjects. Other authors state that deep S waves in all standard limb leads

may occur in normal subjects (3, 11, 20), but they included electrocardiograms in which the S waves were not deep enough to make the QRS complexes predominantly negative.

Most authors are of the opinion that this limb-lead pattern is due to the position of the heart within the thorax (2, 4, 9, 10). Hurwitz, Langendorf, and Katz (6, 7) attributed this pattern merely to combined left and right ventricular "strain" on the basis of a single necropsied case, but admitted that in some cases it may be due to the position of the heart within the thorax. Burstein and Ellenbogen (1) related this pattern to the presence of pleural and pericardial effusions. In 3 of their cases the electrocardiographic pattern returned to normal when the effusions disappeared. Fox, Sokol, and Bernstein (2) showed that change in the position of the patient or the presence of a pneumothorax would alter this limb-lead pattern. This was not true of Case 6 in the present series, probably because extensive intrathoracic tuberculosis immobilized the heart. Gardberg and Ashman (3) and Goldberger and Schwartz (5) concluded that this pattern is due to backward displacement of the apex in a vertical heart.

Of the 6 cases in the present series, 4 patients had apparently normal vertical hearts on clinical grounds but there was an extracardiac factor present (right thoracoplasty or funnel chest) which could influence the position of the heart. The other 2 patients had vertical hearts and chronic cor pulmonale.

With respect to patients with right ventricular enlargement (chronic cor pulmonale), there is evidence that points to altered position of the heart as the cause of the standard limb-lead pattern under discussion. In a recent analysis of causes of right-axis deviation, Kossmann and associates (8) believe that right-axis deviation (of which this pattern can be an extreme form) is dependent on the position of the heart within the thorax and they believe that in "certain diseases characterized by a large right ventricle and conditions in the thorax which favor rotation of the heart about its long axis . . . extreme rotation of this organ with almost complete reversal of the electrical fields of the two ventricles in the thorax may occur."

The position of the heart within the thorax is the common denominator for both categories in the classification of these cases given above. The value of multiple precordial leads lies in the fact that the pattern of QRS complexes and T waves across the chest varies with the position of the heart. In both normal and abnormal hearts which present this limb-lead pattern, the precordial leads show a shift of the transitional zone to the left and, since the transitional zone reflects the electrical position of the interventricular septum in relation to the anterior chest wall, this shift to the left must signify a clockwise rotation of the heart on its longitudinal axis, in the absence of any mediastinal shift. Deep S waves become a prominent feature of the precordial leads, particularly on the left side of the precordium, and these may be deflected to the limb leads. In the case of the normal heart, one must look for some extracardiac factor which may cause the heart to rotate clockwise, e.g., right thoracoplasty. In the case of the abnormal heart, right ventricular enlargement will cause the heart to rotate clockwise and the precordial pattern may be complicated by the effects of the

right ventricular hypertrophy as in Case 5 (figure 1), i.e., a late R wave in the right precordial leads.

The prognosis of patients who exhibit prominent S waves in all standard limb leads is poor and depends upon the nature of the complicating disease. Five of the 6 patients described here are now dead and their ages at the time of death varied from 29 to 57 years. Two of the 5 patients died soon after their electrocardiograms were made and the other 3 died 4 to 9 years later, or at the age of 40 to 43 years, well ahead of the normal life expectancy. This is explained by the facts that all patients suffered with far advanced pulmonary tuberculosis and 2 had chronic cor pulmonale.

SUMMARY AND CONCLUSIONS

In 6 cases of a total of 2,850 tracings, there was found the rare electrocardiographic pattern consisting of predominantly negative QRS complexes due to deep S waves in all standard limb leads. These cases are analyzed from an electrocardiographic and clinical standpoint. Multiple precordial-lead patterns in 2 cases are emphasized in order to support the concept that this limb-lead pattern is due to clockwise rotation of a vertical heart around its longitudinal axis. This rotation of the heart was associated with either right ventricular enlargement or a chest deformity in this series of cases.

SUMARIO Y CONCLUSIONES

Electrocardiogramas con Ondas S Sobresalientes en Todas las Derivaciones Corrientes en los Miembros. Patrones Asociados en las Derivaciones Precordiales Múltiples

En 6 casos entre un total de 2,850 electrocardiogramas, se observó el raro patrón formado por complejos QRS predominantemente negativos debidos a ondas S profundas en todas las derivaciones corrientes en los miembros. Esos casos son analizados clínica y electrocardiográficamente. Se hace hincapié en los patrones de derivaciones precordiales múltiples en 2 casos para prestar apoyo al concepto de que ese patrón de derivación en los miembros procede de rotación hacia la derecha de un corazón vertical alrededor de su eje longitudinal. Esta rotación cardíaca se asoció en esta serie de casos ya con hipertrofia del ventrículo derecho o deformidad torácica.

Addendum

Since this paper was submitted for publication, another case has been observed in a 45-year-old Japanese male with far advanced pulmonary tuberculosis involving both lungs, atelectasis of the right lung, mediastinal shift to the right, and clinical evidence of right ventricular failure. Electrocardiogram showed deep S waves in all standard limb leads and also in all precordial unipolar leads from V_1 to V_6, associated with flat T waves in all leads. Autopsy several weeks later revealed chronic cor pulmonale, atelectasis of the right lung, and organizing thrombosis of the right pulmonary artery. This case falls into both categories in the classification given above since the position of the heart within the thorax is influenced by both the right ventricular enlargement and the extracardiac factor of mediastinal shift.

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A STUDY OF 200 CASES OF TUBERCULOUS PLEURISY WITH EFFUSION[1]

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INTRODUCTION

It has been stated (1) that, although ordinary pleurisy with effusion is practically always tuberculous, it represents a relatively light and curable phase of the disease. Although this concept is still held by many clinicians, the results of the present study indicate that tuberculous pleurisy with effusion is a serious phase of tuberculosis and is frequently associated with hematogenous spread of the disease.

In a discussion of pleurisy with effusion, Rubin (3) states, "Statistics concerning the incidence of the various types of pleural effusions are unreliable because much depends on the material studied." The majority of writers discussing pleural effusion in recent literature include only that group of cases in which, at the time of the discovery of the effusion, no evidence of a parenchymal lung lesion was demonstrable. The following paper is the result of the study and analysis of pleural effusions occurring spontaneously with or without pulmonary or extrapulmonary tuberculosis.

COMPOSITION OF CLINICAL SERIES

Selection of case material: Included in this survey are all patients in the Mountain Sanatorium between January 1, 1939 and July 1, 1947 who came into one of the following three groups: (*1*) Patients admitted with a diagnosis of spontaneous or idiopathic pleural effusion, with or without other evidence of tuberculosis, and in whom the known nontuberculous causes for the effusion had been eliminated. (*2*) Patients admitted with pulmonary or extrapulmonary tuberculosis and who during their hospital stay developed a spontaneous pleural effusion. (*3*) Patients who previously had an "idiopathic" pleural effusion, the diagnosis being made by a physician. (All except one in this group had a hospital stay for this illness.)

The inclusion of patients with a preceding pulmonary lesion is admittedly open to controversy. As has been pointed out by Yater (4), Coope (5), Hamman (6), and Farber (7), in the great majority of cases the onset of idiopathic pleural effusion, particularly under the age of forty, is a manifestation of a tuberculous focus seen or unseen in the body. This focus may be extremely small, and one cannot assume it is absent simply because of failure to visualize it on the roentgenogram either because of its minute size or because of its location behind a rib, heart, or behind the effusion itself. Moreover, the onset of a pleural effusion is

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frequently the presenting evidence of a primary infection or an immediate post-primary spread (8, 9), and the presence of effusion must be considered as evidence that a tuberculous focus is present somewhere in the body. The essential disease is, therefore, tuberculosis, whether or not a focus can be shown radiologically. It was believed that there was no fundamental difference between those cases in which a tuberculous lesion was proved prior to the onset of the effusion and those in which no lesion could be demonstrated radiologically. Consequently both groups are included in the statistics.

Distribution of cases by sex, age, and race: Of the 200 patients reviewed, there were 107 males and 93 females. The average age was 25.3 years and the mean age was 20 years. Fourteen patients died (9 males, 5 females), and in this group the average age at the time of the onset of effusion was 33 years. The racial distribution is listed in table 1.

There were 101 right pleural effusions; 80, left; and 19 bilateral effusions. As

TABLE 1

Racial Distribution in Patients with Pleurisy with Effusion

RACE	NUMBER OF PATIENTS
Chinese	4
Native Indian	3
Italian	4
Japanese	6
Slavic	15
French Canadian	20
Irish	29
Scottish	27
English	62

will be shown later, the side involved had no relation to the complications or eventual prognosis.

CLINICAL FEATURES

Symptoms: The onset was acute in 147 patients, insidious in 28, and chronic in 6 patients. The remaining 19 patients had bilateral involvement and, considered as 38 separate episodes of involvement, the onset was acute in 31 and insidious in 7. Sixty patients were able to name a definite tuberculous contact.

The clinical picture heralding the onset of pleural effusions is well known. Pain, mild elevation of temperature, general malaise with fatigue, chills, sweats, and some dyspnea were by far the commonest symptoms. Thirty-seven patients, however, had had no pain; in 6, a history of hemoptysis was elicited; and one was admitted following a very acute onset with high fever and delirium. It is worthy of emphasis that approximately 10 per cent of these patients experienced intermittent chest pain preceding the onset of the effusion by three to six months. This picture was typically represented by the following case histories.

Case Reports

Case 1. F. P., a 20-year-old male, had had no significant previous illnesses and had been in his usual good health until March 1941 when he developed pain in his right chest. The pain was worse on inspiration and was aggravated by coughing and sneezing. Physical examination was essentially negative. There was no elevation of temperature. A chest roentgenogram taken at that time was said to be within normal limits. A diagnosis of pleurodynia was made and, following conservative treatment, the pain ceased. This same sequence recurred in July of the same year. Again it was diagnosed as pleurodynia and again was relieved with symptomatic therapy. In September 1941 the pain returned, this time with fever, dyspnea, and cough. A tuberculin skin test was positive. Physical examination and a roentgenogram of the chest showed the presence of a pleural effusion on the right, and the patient was admitted to the Mountain Sanatorium. Two months later a minimal parenchymal tuberculous lesion was noted in the apex of the lung on the same side as the effusion. The patient left against advice after 130 days of sanatorium care.

Case 2. Miss B, a 21-year-old student nurse, had been in good health all of her life. In January 1945 and again in June of the same year, she had negative chest roentgenograms and negative tuberculin skin tests. In August 1945 she developed pain in the right chest. A tuberculin skin test and chest roentgenogram were not taken at that time. The pain disappeared spontaneously. A routine roentgenogram of the chest, taken in November of the same year at a time when the patient appeared to be in perfect health, showed a pleural effusion on the right side. The tuberculin skin test at that time was positive.

FIG. 1. Diagrammatic reproduction of sizes of effusion: left—Class I; center—Class II; right—Class III.

This clinical picture has been emphasized frequently in the past and is familiar to all. Barnwell (10) states:

A recent persistent pain may be the initial symptom of any of the thoracic maladies responsible for pleurisy. The pain may exist constantly or intermittently for weeks or months before the cause is determined. In primary tuberculosis, pleurisy with effusion may be preceded by pain for several months before the cause is demonstrable by physical examination or X-ray. Pleural pain is often dismissed as pleurodynia, a presumed entity. All pleural pain deserves thorough study until its cause is found or prolonged observation has rendered its significance less.

Features of the pleural effusion: Before any tabulation or analysis was begun it was thought necessary to draw up an arbitrary scale dividing patients into three categories according to the extent of their effusions. This classification is based on the conventional anterior-posterior 54-inch chest roentgenogram and is illustrated diagrammatically in figure 1.

Class I—*Small effusion.* The shadow caused by the effusion does not exceed in area the space limited by a line drawn from one-quarter of the way medially from the lateral margin of the diaphragm to one-half the way up the costal margin.

Class II—*Effusion of medium extent.* The fluid is greater than it is in Class I, but does not exceed the area included in a line drawn from the mid-point of the diaphragm to the junction of the costal margin and the clavicle, or the equivalent of that area.

Class III—*Massive effusion.* Any fluid that is greater in extent than that in Class II.

In the 200 cases studied, small effusions, no matter how slight in extent, were potentially just as dangerous as the most massive effusions. In those patients who developed bilateral effusions, the size of the initial effusion was of no value in determining whether or not that particular patient would develop bilateral effusions. As indicated in table 2, the ultimate mortality rate in the patients having a Class I effusion was just as great as that in patients having a Class III effusion.

In discussing the causes of the size of effusions, Pagel (9) states that the fundamental difference between pleurisy of hematogenous origin and that of broncho-

TABLE 2

Ultimate Mortality Compared with Size of Pleural Effusion

EXTENT OF EFFUSION	NUMBER OF PATIENTS	NUMBER OF PATIENTS NOW DEAD
Small (Class I)*	48	5
Medium (Class II)	79	4
Massive (Class III)	44	4
Bilateral	19	1

*See text.

genic or pulmonary origin is that in the former a very small lung focus may cause extensive pleurisy with effusion, or this may even occur with no lung focus at all. In the bronchogenic or intrapulmonary type, however, the pleurisy varies directly with the extent and behavior of the intrapulmonary focus.

Type of fluid: The appearance of the fluid in the great majority of cases was the usual clear straw color. Three cases showed clear red bloody fluid persistently. The bacteriologic examination was not available in 126 cases. Positive reports for tubercle bacilli were returned in 21 of the 74 cases in which cultures of the fluid were made. Barnwell (10) states, "The single culture of a small amount of sediment from a small amount, 10 to 15 cc., of fluid has given many negative results in the past. The more recent practice of repeatedly culturing large amounts of fluid, 100 to 500 cc., has resulted in the detection of tubercle bacilli in approximately 70 per cent of young persons."

For the purpose of this investigation it is perhaps unfortunate that a more complete bacteriologic report on the pleural fluids was not available. Since many of those patients who had negative fluid cultures went on to develop other tuberculous foci, both hematogenous and nonhematogenous, it would appear that the

finding of a positive or a negative pleural fluid culture has little or no bearing on the prognosis.

Radiological clearing of the effusion: Complete clearing was interpreted on a roentgenogram of the chest in which there was a sufficiently clear costophrenic angle, smooth diaphragm, and no pleural thickening so that one would not suspect that pleurisy had previously been present. Thirty-five patients showed complete clearing, 82 had blunting of the costophrenic angle, and the remainder had moderate to extensive pleural fibrosis. Complete clearing occurred more frequently in those patients who had one or more aspirations.

Development of lesions of the lung parenchyma: Of the 200 cases studied, 92 developed pulmonary tuberculosis. This was diagnosed from the chest roentgenogram taken because of the pleural effusion or developed subsequent to the onset of the effusion. In addition, 10 patients developed clinically recognizable tuberculosis of other organs without evidence of involvement of the lung. Thus,

TABLE 3

Extent and Distribution of Subsequent Pulmonary Lesions

Extent of the Parenchymal Lesion	
Primary tuberculosis	11
Secondary tuberculosis	
Minimal	65
Moderately advanced	30
Far advanced	15
Distribution of the Parenchymal Lesion	
Same side as the effusion	72
Bilateral	42
Opposite side only	7

102 (51 per cent) of the patients developed active tuberculosis. It should be stressed that this figure is perhaps conservative, since the post-sanatorium follow-up on some patients was of necessity incomplete. Twenty-nine patients had parenchymal tuberculous lesions of the lung preceding the effusion. In those who developed pulmonary tuberculosis following the effusion, the average time interval between the two events was 10.3 months, with extremes of one month to seven years.

In table 3 are shown the extent and location of pulmonary lesions in the group of 121 patients who developed these lesions.

Hematogenous extrapulmonary tuberculosis: That pleurisy with effusion is occasionally associated with hematogenous spread of tuberculosis is well known. In this series, 37 patients (18.5 per cent) developed lesions classifiable as hematogenous in origin. The time interval between the onset of the effusion and the development of the hematogenous extrapulmonary tuberculosis varied from one month to 18 years, the average being 21.2 months.

TABLE 4

Organs Involved in 37 Patients Who Developed Hematogenous Complications

ORGANS INVOLVED	NUMBER OF PATIENTS
Genitourinary tract	9
Bones	
Spine	8
Knees	2
Femur	1
Meninges	4
Cervical lymph nodes	3
Breast	1
Anterior chest wall	1
Peritoneum	8
Fallopian tubes	2
Adrenals	1
Meninges (suspect)	1

Obviously some of the above patients had several of the complications listed. Custer and Evans (11) state that it does not seem likely that pleural effusion is the immediate result of hematogenous infection. Since in this series almost 20 per cent developed extrapulmonary tuberculosis, hematogenous in origin, it would appear that pleurisy with effusion may often be the immediate result of hematogenous infection. One of the most striking histories to illustrate this point is given below.

Case Report

Case 3. E. D., a 45-year-old male, had been in good health until he began to complain of persistent cough, dyspnea, chest pain, and fever. This lasted for about five weeks. At that time a chest roentgenogram was taken and a right pleurisy with effusion was diagnosed. The tuberculin skin test was strongly positive. On admission to the sanatorium a diagnostic thoracentesis was done and the fluid was positive on culture for tubercle bacilli. With no further aspirations, the fluid absorbed rapidly. Unfortunately this patient left against advice after 242 days. Twelve months later he began to complain of pain and swelling in his right knee and wrist. A chest roentgenogram at this time showed some infiltration in the apex of the right lung, and he was readmitted to the sanatorium. He was diagnosed as having tuberculosis of the right lung, right wrist, and right knee. Three weeks after admission he developed sudden and persistent attacks of nausea and vomiting relieved by intravenous saline. The blood pressure dropped to 80 systolic and 50 diastolic. He appeared very weak and fatigued. At this time a diagnosis of Addison's disease was considered. The patient seemed to improve slowly; but three weeks later he developed crampy abdominal pain, vomiting, diarrhea, and extreme fatigue. Three days later he became very drowsy, and he died in his sleep that night. A diagnosis of Addison's disease was made. No autopsy permission was granted.

The figure of 18.5 per cent given for the occurrence of hematogenous complications may prove to be conservative, as will be commented on later.

Analysis of Deaths

At the time of writing 14 deaths had occurred, 9 males and 5 females having succumbed. The average stay in the hospital for the treatment of the effusion, or of its complications if occurring during the same admission, was 343 days. The causes of death were the following:

Tuberculous meningitis—4 deaths
Tuberculous peritonitis—3 deaths: Terminally, one of these patients had miliary spread of the disease.
Far advanced pulmonary tuberculosis—2 deaths
Far advanced pulmonary tuberculosis with tuberculous enteritis—2 deaths
Intestinal obstruction following tuberculous enteritis, associated with tuberculosis of the spine and kidney—1 death
Addison's disease, associated with tuberculosis of the knee and wrist—1 death
Cause of death uncertain—1: This patient was a known diabetic under control. Patient suddenly developed severe diarrhea, tachycardia, dyspnea, and died.

As stated earlier, it is thought that, whether or not a pleural effusion presents itself before, concurrently with, or following the onset of a pulmonary parenchymal lesion, the disease process should be considered to be a serious one, and may possibly be indicative of the eventual occurrence of hematogenous spread of tuberculosis.

Treatment

The primary principle in the treatment of the patients in this series was a sanatorium regimen of bed rest. The value of repeated aspirations in pleural effusion is controversial. One writer (12) states that inhibition of resorption of the exudate is released by the trial puncture itself. This would seem to be corroborated in this series inasmuch as the removal of only 1 to 50 cc. resulted in a slightly higher percentage of complete pleural clearing than occurred in the group who had no aspirations. Others (13) practice complete drainage as soon as any reasonable amount of fluid has accumulated, as much as two liters at one time. Young and Beaumont (14), however, suggest aspiration under the following conditions: (a) if the fluid is causing positive pressure; (b) if no absorption is evident after fourteen days; (c) if there is acute pulmonary edema; and (d) in some cases of large bilateral pleurisy with effusion. It should be noted that none of the reports in which vigorous aspiration was recommended included any long-term results. Vigorous aspiration may well be the most rapid way of removing the fluid but the effect of this on the course of the tuberculosis over a five- or ten-year period is debatable.

A satisfactory analysis of the treatment was extremely difficult to make since there seemed to be an almost limitless number of variables to consider. As a result, it was decided arbitrarily to divide the patients into four groups on the basis of the amount of fluid removed from the chest. It must be emphasized that in this analysis no consideration is given to such factors as the original size of the effusion or the existence of underlying tuberculosis. The data thus obtained are presented in table 5.

A study of the above chart shows that there is no apparent correlation between the amount of fluid aspirated and the eventual prognosis or the complications encountered. Even the absence of any more specific conclusion on this point is perhaps of value. In other words there is no apparent "rule of the thumb." Each case must be assessed clinically on its own merits before recommending or refusing to recommend aspiration.

Since pleural effusions may be indicative of hematogenous tuberculosis, the use of streptomycin would appear to be valuable. Only one patient in this series was treated with streptomycin and in that case it was used because of the suspected presence of tuberculous meningitis.

TABLE 5

Ultimate Course of Disease in Relation to Thoracentesis—Events in Subsequent Course

VOLUME OF FLUID REMOVED BY ASPIRATION	NUMBER OF PATIENTS	AVERAGE DAYS IN SANATORIUM	PARENCHYMAL DISEASE DISCOVERED AFTER ASPIRATION	POSITIVE SPUTUM	HEMATOGENOUS DISSEMINATION	COMPLETE CLEARING OF EFFUSION	DEATHS	LATER BREAKDOWN	REMAINING IN SANATORIUM
0	87	380	9	30	16	16	8	9	7
1 to 50 cc.	14	316	1	2	2	4	1	1	0
51 to 500 cc.	22	292	7	10	5	5	0	3	1
Over 500 cc.	36	454	7	13	6	3	3	6	2

Note: Except for column 3, the numbers refer to patients. The history of aspirations was incomplete in 41 patients and they were not included in the table.

Late Follow-up

As previously noted, many of the patients studied were treated at Mountain Sanatorium during the war years of 1939 to 1945. A few were members of the armed forces of Norway and Great Britain and have since returned to their home countries. For purposes of this analysis, it was assumed that those patients from whom nothing has been heard are at present alive and well. If any of this group has had a relapse or developed a complication of his disease, the event would serve to reinforce the thesis of this paper. It is therefore possible that the estimated frequency of hematogenous and nonhematogenous spread of tuberculosis, as well as the number of deaths, may prove to be erroneously low.

CONCLUSION

Two hundred consecutive cases of pleurisy with effusion, with or without other tuberculous foci, have been reviewed and the following points have been emphasized:

1. Pleurisy with effusion represents a relatively serious phase of tuberculosis, and may at times be an early manifestation of an ultimately fatal infection. In this series, 51 per cent of the patients presenting signs, symptoms, and roentgenographic evidence of pleurisy with effusion developed pulmonary or extrapulmonary tuberculosis. Eighteen and five-tenths per cent developed evidence of hematogenous dissemination of the disease.

2. Intermittent chest pain, even with a normal chest roentgenogram, should be followed by serial roentgenograms and tuberculin skin tests for six to nine months.

3. The size of the effusion and the side involved apparently have no direct bearing on the complications to be encountered or the resulting prognosis. In more than 50 per cent of the patients with bilateral pleural effusion, however, hematogenous dissemination of the disease occurred.

4. Whether the pleural effusion begins before, concurrently with, or after a parenchymal tuberculous lesion, or even if it occurs with no visible parenchymal lesion whatsoever, it should be considered as evidence of a possible hematogenous dissemination of tuberculosis.

5. An analysis of the therapeutic value of aspirations was inconclusive. Bed rest under a sanatorium regimen, diagnostic aspiration, followed by treatment of any underlying focus, are all requisite. Repeated aspirations may be indicated in certain cases. At the present time it appears that streptomycin will be used in many cases of this type.

CONCLUSIONES

Estudio de 200 Casos de Pleuresía Tuberculosa con Derrame

Tras el repaso de 200 casos consecutivos de pleuresía con derrame, con o sin otros focos tuberculosos, recálcanse los siguientes puntos:

1. La pleuresía con derrame representa una fase relativamente grave y a veces letal de la tuberculosis. En la serie estudiada, 51 por ciento de los enfermos que mostraban signos y síntomas y datos radiológicos de pleuresía con derrame presentaron signos de difusión hematógena de la enfermedad.

2. La presencia de dolor torácico intermitente, aun con una radiografía torácica normal, debe ir seguida de radiografías seriadas y de cutirreacciones con tuberculina por espacio de seis a nueve meses.

3. El tamaño del derrame y el lado afectuado no guardan aparentemente relación con la complicación que va a encontrarse o el pronóstico. Sin embargo, más de 50 por ciento de los enfermos con derrame pleural bilateral manifestaron tuberculosis hematógena.

4. Ya comience el derrame pleural antes de, junto con, o después de, una lesión tuberculosa del parénquima, y aun presentándose sin la menor lesión visible del parénquima, hay que considerarlo como signo de posible diseminación hematógena de la tuberculosis.

5. Un análisis del tratamiento en lo relativo a aspiraciones fué poco terminante. El descanso en cama bajo régimen sanatorial, la aspiración para diagnóstico, seguida del tratamiento de todo foco subyacente, todos ellos son necesarios. En ciertos casos, pueden estar indicadas las aspiraciones repetidas. En la actualidad, parece que se usará la estreptomicina en muchos casos de este género.

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Case Reports

MASSIVE PULMONARY HEMORRHAGE IN TUBERCULOSIS[1,2]

A Report of Two Unusual Cases

GRANT N. STEMMERMANN AND OSCAR AUERBACH

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INTRODUCTION

Massive hemorrhage from a pulmonary artery is a common cause of sudden death in patients with pulmonary tuberculosis of long duration. The bleeding usually occurs from an aneurysm of a pulmonary artery within the wall of a tuberculous cavity. The 2 cases we are presenting are unusual in that in each case the bleeding site abutted an extrapulmonary space. In neither case was an aneurysm found at the point of rupture. The writers believe that these cases serve to emphasize defense mechanisms that prevent similar hemorrhages from occurring within the lung during the early stages of this disease.

CASE REPORTS

Case 1. A 56-year-old white, male, bank messenger first became ill in the fall of 1947, at which time he noted a worsening of a long-standing cough. In December of the same year he developed high fever and sharp chest pain. Sputum smears at this time revealed the presence of acid-fast bacilli. He was admitted to the Halloran Veterans Administration Hospital in March 1948.

The admission roentgenogram revealed patchy, confluent densities in the left upper lobe with a small cavity projected through the second rib anteriorly. Similar confluent and patchy densities were present behind the left heart. Direct smear of the sputum was positive for acid-fast bacilli (Gaffky IX). He received a six-week course of streptomycin. His temperature returned to normal, his appetite increased, and his sputum decreased moderately in amount. A left pneumothorax followed by pneumonolysis failed to close the cavity. Bronchoscopy revealed an ulcer at the carina. Since the infecting organism was still sensitive to less than 1 γ of streptomycin, he was given an additional six-week course of streptomycin. Follow-up bronchoscopy in February failed to reveal the carinal ulcer. On April 7, 1949, fifty-two days after the termination of streptomycin therapy and fifteen months after the onset of his tuberculosis, the patient had a sudden overwhelming hemoptysis. He went into shock and died within ten minutes.

Necropsy Findings

Gross examination: The mouth, tracheobronchial tree, esophagus, and stomach were filled with bright red blood. A cavity, measuring 4 cm. in its greatest diameter, was present in the posterior aspect of the upper lobe of the left lung. Its wall was from 2 to 4 mm. thick. No aneurysmal dilatation of a pulmonary artery within its wall was discovered. A

[1] From the Laboratory Service, Halloran Veterans Administration Hospital, Staten Island 2, New York.

[2] Sponsored by Veterans Administration and published with approval of Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

branch of the upper lobe bronchus opened widely into this cavity. The bronchial lining between the bronchocavitary junction and the carina was ulcerated. The base of the ulcer was thrown into rounded folds and lined by caseous material. The cartilagenous plates of the left main bronchus were exposed in the floor of the ulcer. The left pulmonary artery was firmly fixed to the main stem bronchus. At the bifurcation of the vessel into the upper and lower lobe bronchus the arterial lumen communicated with that of the bronchus. Attached to the intimal surface of the artery at the edge of this region was a small, friable, gray-red clot. Ulcers were present on the right true vocal cord and throughout the trachea. These varied from 3 mm. to 2.5 cm. in diameter. The bases of some of these ulcers were smooth, whereas others had a red granular appearance. Numerous encapsulated, caseous foci were present throughout all lobes of the lungs.

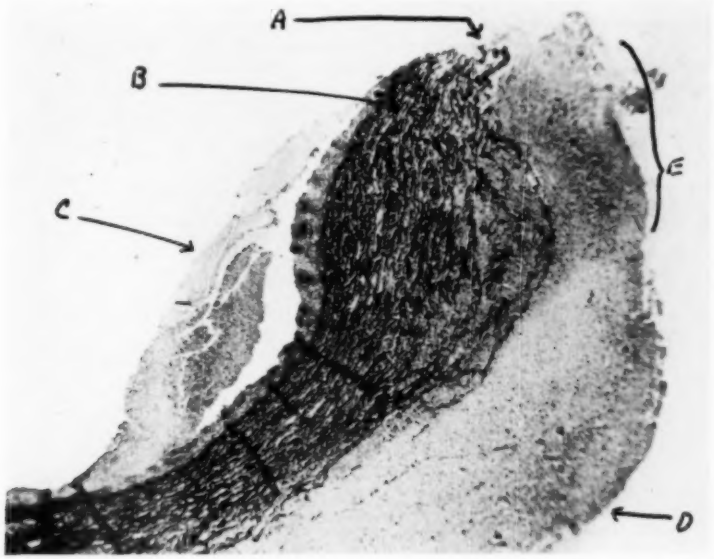

FIG. 1. Case 1. A. Junction of fused artery and bronchus at rupture site. B. Media of pulmonary artery. C. Intimal surface with clot. D. Lining surface of bronchus. E. Area where zone of caseation extends through entire thickness of bronchus and artery.

Microscopic examination: The left main bronchus was lined for the most part by a layer of pink-blue granular material (caseation). Beneath this was a pyogenic membrane composed of fibrin, polymorphonuclear leukocytes, and, towards the periphery, fibroblasts. Beyond this was a broad vascular granulation tissue composed of epithelioid cells, fibroblasts, plasma cells, and lymphocytes. At one point the ulcer extended through the bronchial wall to involve the pulmonary artery. The entire arterial wall at this point had a pink-blue granular appearance (caseation). The elastic fibers in this region remained intact and were well demonstrated in sections stained by the Elastica-van Gieson method. At a point corresponding with the rupture site observed grossly, the tissues of all coats of the vessel, including the elastic fibers, had a fragmented appearance. The necrotic vessel wall adjoining the perforation was lined by a narrow layer of fibrin, polymorphonuclear leukocytes, fibroblasts, and collagen fibers. Contained within the adjacent intact intima were histiocytes, polymorphonuclear leukocytes, fibroblasts, and collagen fibers. The blood clot covering the zone of caseation was attached to the intima at this point (figure 1).

Some of the tracheal ulcers were lined in part by stratified squamous epithelium. The excavation in the upper lobe of the left lung had extended to include several older encapsulated foci within its wall.

Case 2. A 32-year-old white man had pleurisy on the right side in November 1946. A roentgenogram of the chest in October of the same year revealed the presence of tuberculosis in the upper lobe of the right lung. In September 1947 cavities were demonstrated in the upper lobe of the left lung. He was admitted to Halloran Veterans Administration Hospital in December 1947. In August 1949 a right upper lobectomy was performed. This was followed by a bronchopleural fistula and hydrothorax. The fistula closed and the right chest became "stabilized." In October 1949 a left upper lobectomy was performed. On the eleventh postoperative day he developed a bronchopleural fistula, followed by a mixed infection empyema. Acid-fast bacilli were present in smears of the empyema fluid. The empyema failed to clear despite streptomycin therapy and suction drainage. There were several transient episodes of hemorrhage, during which blood was coughed up by the patient as well as aspirated from the pleural space. On January 10, 1950 the patient sustained a severe pulmonary hemorrhage and died within three minutes of its onset.

Necropsy Findings

Gross examination: On opening the chest the left pleural space was found to contain 500 cc. of fluid and clotted bright red blood. The parietal pleura was thickened and opaque. The left pleural space was obliterated posteriorly. Anteriorly and basally the space was traversed by shaggy gray bands of tissue. The intervening surface of the visceral pleura was covered by a thin, gray-white film. Within the anteromedial aspects of the pleural space and 1.5 cm. below the left main bronchus there was an enclosed pocket surrounded by visceral and parietal pleura. This measured 3 cm. vertically, 1 cm. mediolaterally, and 2 cm. anteroposteriorly. It was filled with blood and its lining was covered by a friable, gray-white material. The wall of the space was 3 mm. thick in both its visceral and parietal aspects. The lower lobe bronchus communicated with the small space through a 4 mm. opening, while the stump of the left upper lobe bronchus opened widely into the empyema space surrounding the remainder of the lung. A large medial branch of the lower lobe bronchus communicated, through a 3 mm. opening on its medial surface, with the small enclosed pocket in the anteromedial aspects of the pleural space. This opening was 7 mm. from the origin of the vessel in the main artery to the left lower lobe.

The right pleural space contained 200 cc. of creamy yellow fluid. The space was obliterated posteriorly. Where the space was patent the pleurae were covered with a thin, gray-white film.

The tracheobronchial tree was filled with bright red, fluid blood. Encapsulated caseous foci and acinous nodose foci were scattered through both lower lobes. No other significant findings were noted in the gross examination of the body.

Microscopic examination: As the lower lobe pulmonary artery was traced towards the rupture site, the intima gradually became thicker until it attained a maximum depth of approximately 200 microns. This thickened portion was composed of dense collagenous tissue containing occasional fibroblasts and plump endothelial cells. Just proximal to the rupture site the media was replaced by granulation tissue (figure 2). The latter was rich in collagen fibers and contained fibroblasts and histiocytes. Towards the luminal surface this tissue blended with the thickened intima. An Elastica-van Gieson stain showed that the elastic fibers gradually tapered away and then disappeared in the granulation tissue which replaced the media. The pleural space was lined by a wide pyogenic membrane composed of fibrin, polymorphonuclear leukocytes, erythrocytes, and nuclear debris. This layer ended abruptly at the rupture site. Beneath the pyogenic zone was a zone of granulation tissue which blended with tissue of like nature described above as replacing the media and adventitia of the artery. For this reason it was difficult to delineate the edge of the vessel from the thickened pleura. At this point the lumen of the empyema pocket and the artery communi-

cated freely with one another. Present within the pleural granulation tissue and within the adjacent lung parenchyma were many small round foci composed of epithelioid cells Langhans' giant cells, fibroblasts, and collagen fibers.

Microscopic examination of other portions of the small empyema pocket revealed that in some aspects it was lined by a wide layer of caseous material. In its deeper portions it resembled the portion already described.

Encapsulated caseous foci and acinous nodose foci were present in both lower lobes. Some of the latter were considered of recent origin whereas others showed advanced healing changes. Miliary foci were present in the spleen, liver, right kidney, and right adrenal gland.

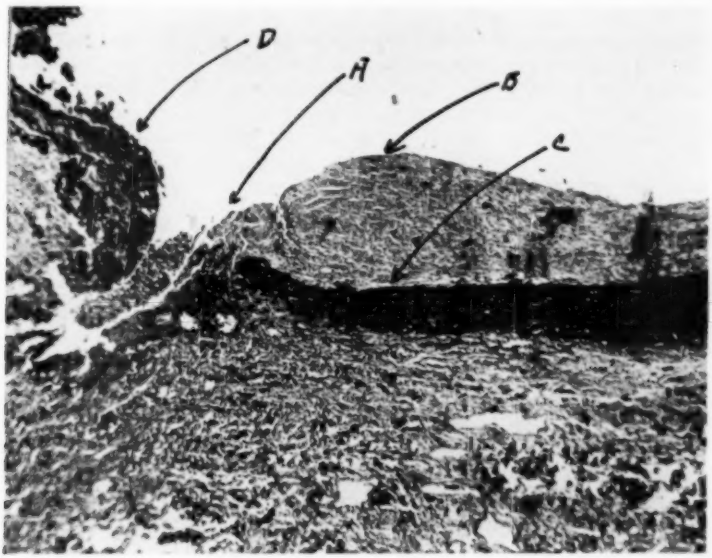

FIG. 2. Case 2. A. Rupture site. B. Thickened intima of pulmonary artery. C. Media. D. Lining of empyema cavity.

DISCUSSION

Lethal pulmonary hemorrhage in patients with pulmonary tuberculosis is usually observed in those patients whose disease is of long standing (5, 8) and it generally results from rupture of a pulmonary artery aneurysm into a cavity. Defenses within pulmonary arteries are sufficient to keep hemorrhage at a minimum during early stages of the disease. The most important of these defenses is an obliterative endarteritis which so narrows the lumen of the vessel that massive hemorrhage does not occur if its wall is destroyed. The mechanism of this defense is best understood after a study of the manner in which pulmonary arteries are destroyed by progressing tuberculous lesions.

Pulmonary arteries are attacked in two different ways. The commonest of these is seen adjacent to slowly expanding tuberculous excavations. Menetrier (1) in 1890 and Eppinger (2) in 1887 made thorough studies of the vascular changes adjacent to such cavities. They observed that as a vessel is traced towards a cavity wall the adventitia

and media are replaced by granulation tissue which destroys and replaces these coats. They noted that if the cavity continues to expand, or if the vessel is traced deeper into the cavity, this granulation tissue is replaced by a zone of caseation. They also observed changes within the intima of the vessel. The intima becomes thickened in that portion of the circumference of the vessel which is nearest the tuberculous lesion. They observed that this change occurs before either of the external coats is altered. Menetrier believed that the thickened intima consisted of flat cells, a fibrillar substance, and occasional migrating cells. Eppinger could not determine whether the intimal proliferation was derived from endothelial cells or connective tissue. Both authors noted a progressive increase in the thickness of the intima as the vessel was traced towards the cavity. This thickening either obliterates or greatly narrows the lumen of the vessel before the media is destroyed, so that the danger of massive hemorrhage is minimized. Should the lumen remain patent, an aneurysmal dilatation into the adjacent cavity can then occur. Rupture of such an aneurysm is the common source of massive hemorrhage in pulmonary tuberculosis. These aneurysms were observed many years ago by Rasmussen (3), Meyer (4), Menetrier (1), Eppinger (2), and by many others. The aneurysms are usually seen along vessels 1 to 5 mm. in diameter. Rupture is usually seen late in the course of the disease. The exact nature and mode of development of these aneurysms has been the subject of some debate. Eppinger (2) and Auerbach (5) believed that after fusion of the vessel with the cavity wall, the fibrin of the inner cavity wall extended through all layers to the intima. Meyer (4) believed that the fibrin extended from the vessel towards the cavity.

If a pulmonary artery is involved in a rapidly progressing caseous process, however, the above sequence of events is somewhat altered. Under these circumstances the resulting caseation necrosis destroys all of the structures within the arterial wall except the elastic fibers of the media. Such vessels are readily identified within the zone of caseation, and if they are studied with Elastica-van Gieson stains the elastic fibers within the media are found to be well stained and not decreased in number. The support of the intact, but necrotic, lung tissue which surrounds the vessel, together with obliterative endarteritis, probably prevents massive hemorrhage at this stage.

In neither of the present cases was an aneurysm found to be the source of hemorrhage. In each case the involved artery was of a larger caliber than arteries which usually adjoin pulmonary cavities. Obliterative endarteritis could not close the larger lumina of the involved arteries, so that the integrity of the vessel walls rested solely upon the adventitia and media.

In the first case the entire thickness of the wall of the left pulmonary artery had undergone caseous necrosis. This resulted from a bronchial disease of far greater severity than that usually seen in tuberculosis. The bronchial lesion showed a tendency to heal while the patient was under streptomycin therapy. Bronchoscopic examinations and epithelialization of the tracheal ulcers furnish evidence of this tendency. Subsequent to cessation of streptomycin therapy, however, the extent and rapidity of spread of the caseous process within the bronchial tree was comparable to that of a fulminating caseous pneumonia. The cartilagenous plates, the peribronchial connective tissue, and the left pulmonary artery were included in the rapidly advancing zone of caseous necrosis. Only the elastic fibers within the media of the vessel were not destroyed in the process. The intact elastic fibers did not offer sufficient resistance to pulmonary arterial pressure to prevent a slough; intact, but fragmented, elastic fibers having been present at the rupture site. One may infer that of themselves these fibers do not offer a very considerable resistance to hydrostatic pressure since the pulmonary blood pressure is not a high one. (Dexter and associates (6) have shown in a control study that the normal pulmonary blood pressure varies from 20/8 to 60/18 mm. of mercury.)

The artery in the second case was affected in a manner similar to that noted adjacent to a slowly progressing pulmonary cavity. At the rupture site the entire thickness of the vessel wall had been replaced by granulation tissue similar to that lining the pleural space (figure 2). The pyogenic membrane which lined the pleural space extended to the inner surface of the vessel, indicating a gradual erosion of the wall from without.

Klosk (7) reported a case similar to those noted above. In his case a massive pulmonary hemorrhage was derived from the main lower lobe branch of the pulmonary artery adjacent to cavity near the hilus of the lower lobe of the left lung. Klosk found no aneurysm, but observed that part of the arterial wall was replaced by tuberculous granulation tissue. The outer third of the media had undergone caseous necrosis. The elastic laminae ended abruptly at either side of the point of rupture and were greatly distorted. He also noted that the endarteritic repair usually seen in similarly diseased vessels was not present and he believed the rupture to be due to the absence of this repair.

We believe that our cases and the case reported by Klosk (7) affirm the importance of the process of obliterative endarteritis in preventing massive pulmonary hemorrhage. Where it has not occurred or where it cannot obliterate a large lumen, even intact elastic fibers are not sufficient to prevent such an occurrence.

SUMMARY

Two cases are reported of patients with pulmonary tuberculosis who died from massive pulmonary hemorrhage. The source of arterial disease in each case was an extrapulmonary lesion. In one case this was a bronchial ulcer, and in the other it was an empyema cavity. In neither case was arterial aneurysm found to be the source of hemorrhage. In each instance, however, the involved artery was of larger caliber than those which usually adjoin pulmonary cavities, so that an obliterative endarteritis could not sufficiently narrow their lumina to prevent massive hemorrhage. These cases emphasize the primary importance of obliterative endarteritis in preventing massive hemorrhage in the early phases of the tuberculosis.

SUMARIO

Hemorragia Pulmonar Masiva en la Tuberculosis: Presentación de Dos Casos Extraños

Los dos casos presentados son de tuberculosis pulmonar en enfermos que fallecieron de hemorragia pulmonar masiva. En ambos la causa de la arteriopatía radicaba en una lesión extrapulmonar, tratándose en uno de úlcera bronquial y en el otro de caverna empiemática. Ni en uno ni otro resultó ser la causa de la neumonorragia un aneurisma arterial. No obstante, en ambos la arteria afectada era de mayor calibre que las que suelen colindar con las cavernas pulmonares, de modo que una endarteritis obliterante no podía estrechar suficientemente la luz de la arteria para impedir la hemorragia masiva. Estos casos recalcan la importancia primordial de la endarteritis obliterante en la prevención de la hemorragia masiva en las fases tempranas de la tuberculosis.

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GASTRIC DILATATION FOLLOWING LEFT PHRENIC INTERRUPTION TREATED WITH URETHANE OF BETA-METHYLCHOLINE (URECHOLINE)[1]

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Gastrointestinal disturbances following phrenic interruption are not uncommon. This complication has been reported by several observers (1–5), and one writer even places the incidence at more than 25 per cent of cases (1). In most instances the symptoms have been comparatively mild, and have subsided following the return of diaphragmatic function. In some instances, however, acute dilatation of the stomach has supervened following this operation, and continuous gastric suction has been required for varying periods of time (2).

The writers are not aware, however, of any drug which has previously been found to be of value in the treatment of this complication. We therefore consider that it may be of interest to report a case which was successfully treated with a parasympatheticomimetic preparation.

CASE REPORT

M. MacC., a 20-year-old white girl, was admitted to Point Edward Hospital on April 13, 1949, with a moderately advanced tuberculous lesion situated in the lower portion of the left lung. On May 15, 1949 a left phrenic crush was performed, and on May 27, 1949 artificial pneumoperitoneum was initiated.

Approximately one month following the phrenic interruption, the patient began to complain of epigastric fullness and discomfort, anorexia, nausea, and vomiting, all of which symptoms gradually increased in severity. It was at first considered that these symptoms were probably due to disturbance of intra-abdominal relations resulting from pneumoperitoneum, and the latter was abandoned on August 25, 1949. Despite this, however, her general condition became worse and her weight, which had been 122 pounds at the time of the phrenic interruption, had fallen to 106 pounds by October 1, 1949.

On October 12, 1949, fluoroscopic and roentgenographic examination following the administration of a barium meal revealed gross dilatation of the stomach, which did not fill completely, even after the ingestion of 750 cc. of barium mixture (figure 1). The stomach was markedly atonic, no peristalsis being visible, but there was no obstruction at the pylorus and the opaque mixture passed slowly but freely into the duodenum and jejunum. The diagnosis of persistent gastric dilatation following a left phrenic interruption was then made. Since the patient's condition continued to deteriorate, it was thought advisable to undertake some form of specific treatment.

It was considered that a certain degree of similarity existed between this condition and that which occasionally follows vagotomy in the treatment of peptic ulcer. Since encouraging results had previously been reported from the use of the urethane of beta-methylcholine in the treatment of gastric dilatation following vagotomy, it was decided to carry out a therapeutic trial of this preparation in the present case.

Accordingly, on October 21, 1949, the stomach was emptied by Levine tube on one occasion, and the patient was given urethane of beta-methylcholine (Urecholine),[2] 5 mg. three times daily before meals. Since no dramatic improvement resulted from this treatment, the dosage was increased to 10 mg. three times daily before meals on October 24, 1949. From this point on, there was steady and continued improvement, although fluoroscopic examination revealed no movement of the left leaf of the diaphragm. The patient's appetite improved, the sensation of epigastric fullness and distress disappeared, and there was no further nausea or vomiting. An increase in weight was noted almost immediately,

[1] From Point Edward Hospital, Sydney, Nova Scotia.

[2] Restricted trade name of Merck & Co., Inc., Rahway, New Jersey.

and at the time of writing the patient weighs 115 pounds, and has no symptoms. Re-examination of the stomach on December 8, 1949, following a barium meal, revealed a stomach of normal size and shape, with normal peristalsis (figure 2). The Urecholine was discontinued on November 8, 1949, after 500 mg. had been administered.

COMMENT

The physiologic explanation of this condition is obscure. The possibility that gastric dilatation may be abolished by the temporary exhibition of a parasympatheticomimetic agent suggests that the mechanism may be a self-perpetuating reflex arc causing vagal

FIG. 1. (Left) Roentgenogram, October 12, 1949, following administration of barium meal, revealing gross dilatation of the stomach.

FIG. 2. (Right) Roentgenogram, December 8, 1949, following administration of barium meal, revealing stomach of normal size and shape.

inhibition. Interruption of this vicious circle at any point, in this case the effector organ, may thus result in the permanent restoration of vagal tone.

Although the occurrence of gastric dilatation following phrenic interruption is not uncommon in centers where this operation is performed frequently, we are not familiar with any previous report of the use of this drug in similar circumstances. It is therefore hoped that further confirmation of the efficacy of this treatment will be forthcoming in the near future.

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Letters to the Editors

DIFFERENTIAL RESPONSE TO METABOLITES OF M. TUBERCULOSIS H37Rv AND H37Ra

To the Editors of the American Review of Tuberculosis:

The following amino acids in concentrations of 0.7 mg. per ml. have been found to have no effect on the growth of *M. tuberculosis*, strains H37Rv and H37Ra: glycine, *l*-arginine, *l*-lysine, *l*-proline, *l*-hydroxyproline, *l*-leucine, *dl*-leucine, *dl*-isoleucine, *dl*-valine, *l*-serine, *d*-threonine, *dl*-ornithine, and *dl*-citrulline. Growth of both strains was stimulated by the following: *l*-glutamic acid, *dl*-aspartic acid, *l*-asparagine, *l*-glutamine, and *l*-histidine. Alpha alanine stimulated H37Ra and had no effect on H37Rv. Inhibition of growth of both strains was obtained with norleucine, *l*-threonine, and *dl*-tryptophane. The following inhibited only H37Rv: *d*-serine, β-alanine, *dl*-phenylalanine, and *l*-tyrosine. Of 17 other metabolites tested none produced stimulation; and only thymine, hypoxanthine, and nicotinic acid had a differential inhibitory effect on the two strains.

Adenosine caused marked inhibition and lysis. Adenine also inhibited, but less effectively, and caused no lysis. H37Ra could be adapted to utilize adenosine as a nitrogen source. The adapted organisms deaminated adenosine but did not utilize the inosine so formed.

Of 21 substances tested, only methionine and choline antagonized the adenine inhibition of growth, the antagonism being complete in H37Rv but only slight in H37Ra. Ten substances had a markedly greater effect on one strain than on the other in the presence of adenine, although no differential action was found when they were tested alone. Since neither pantothenic acid nor β-alanine antagonized *d*-serine, the hypothesis advanced by Davis (Davis, B. D.: Experientia, 1950, *6*, 41) for *E. coli*, that *d*-serine interferes with conversion of β-alanine to pantothenic acid, cannot hold for the tubercle bacillus.

The observations support the hypothesis that H37Rv has capacity to utilize phospholipids which has been lost by H37Ra. They further indicate that in H37Rv at least two pathways for acetylation exist, namely, one via acetate, and the other involving condensation of pyruvate with α-amino acids, only the latter of which is retained by H37Ra.

From the frequency of appearance of H37Ra colonies, from the rates of growth of the two strains, and from the differential response to metabolites of the parent and derived strains, it may be considered that the two differ by a single gene mutation.

The results will be published *in extenso* elsewhere.

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BOOKS

MARK D. ALTSCHULE: *Physiology in Diseases of the Heart and Lungs. Harvard University Monograph in Medicine and Public Health, Number 10, Pp. xv-368, Harvard University Press, Cambridge, Massachusetts, 1949, Price $5.00.*

This small treatise is actually a critical summation of the data concerning the physiological disturbances in the most common diseases of the heart and lungs. About two-thirds of the material deals with the changes in various body functions in chronic cardiac decompensation. In addition, there are chapters on coronary disease, pericarditis, the arrhythmias, and congenital and acquired cardiac defects. About fifty pages are devoted to primary pulmonary affections: asthma, emphysema, fibrosis, pneumothorax, pleural effusion, and pneumonia.

The approach to disease is in terms of physiological derangements. Consideration is given to changes in cardiac output, circulatory and respiratory dynamics, tissue metabolism, and other pertinent functions. It is written in narrative style and is in the nature of a guide to the literature with commentaries. It is full of meat and has to be taken in small portions.

The literature on the pathological physiology of heart failure is replete with controversies. These pertain not only to theoretical concepts but also to the validity and interpretation of data. The author presents most, but by no means all, of the important factual material. His interpretation of the facts, particularly the evaluation of the relative importance of various factors in the genesis of symptoms and signs in congestive heart failure, appears to be slanted in favor of his hypothesis that the basic mechanism is reduced cardiac output in proportion to metabolic needs. Emphasis is placed on the role of the chemical as against the neurogenic factors in cardiac dyspnea.

The references are well indexed immediately after each chapter. The bibliography, while not complete, is perhaps the most important part of the book. Notable among the omissions are the work of Sutton and Lueth and of Rothschild and Kissin on the mechanism of angina, and the important contribution of Starling on the dynamics of cardiac muscle. The student who is interested in the mechanism of the manifestation of cardiac and pulmonary disease and the investigator working in this field will find here a good introduction to the literature.

B. FRIEDMAN

NORVIN C. KIEFER: *Present Concepts of Rehabilitation in Tuberculosis. A Review of the Literature, 1938–1947. Pp. 398, National Tuberculosis Association, New York, Price $3.*

While a senior officer in the Tuberculosis Control Division of the Public Health Service, the author found it necessary to become thoroughly familiar with recent concepts and practices in the field of rehabilitation in tuberculosis. With the aid of the personnel and library facilities of the Public Health Service, 1,007 articles in English were abstracted and their titles listed in a 50-page bibliog-

raphy at the end of the present volume. The abstracts of these articles have been arranged by the author under different chapter headings so that the sanatorium director who wishes to know what agencies deal with rehabilitation, the types of program in operation and their cost, the personnel requirements for rehabilitation staffs, the views of labor and management on the employment of handicapped persons will find the experience of other workers in this field in the United States, England, Russia, and France reported in full. The comprehensive index of subjects in addition to the table of contents makes it possible for the reader to orient himself quickly in the text. A separate index of authors is also appended, although it is not clear why the authors should not have been listed alphabetically in the bibliography in the first place.

The author specifically states that "the first fifteen chapters of the book present a report in which editorial comment is kept at a minimum." In the sixteenth chapter, he presents his own program stressing the need for adequate medical leadership and training. He recommends basic research into activity to be allowed tuberculous patients, adequate statistical study and evaluation of the results of rehabilitation in spite of the obvious difficulties of such a project, further study of the psychological aspects of rehabilitation, and spiritual guidance for the patient.

This book is a useful compendium and reference on present concepts of rehabilitation in tuberculosis. The author's stated intention that editorial comment should not enter into the summary of the articles reviewed has been faithfully carried out. There are those, including this reviewer, who hold a somewhat different view on the manner in which a survey of literature should be presented. An exhaustive bibliography is, of course, essential in a work of this kind and the one appended here makes it possible to look up any specific article on the subject. But what the casual reader cannot do, and hopes the compiler of the bibliography and the expert in this field will do, is to make a critical and comparative evaluation of the work done in the special field. In this book, for instance, it seems to us unfortunate that the chapter on psychological factors in rehabilitation in tuberculosis should report a number of superficial studies without comment as to their inadequacy and probably erroneous conclusions. In other words, we believe that the man who makes a comprehensive review of literature in a given field should be forthright in expressing his own judgment, as his opinion can always be checked by a reference to the original article. If such a forthright point of view is not taken, too much inconsequential material, which should only remain as a title in a bibliography, is repeated and broadcast once again.

BEATRICE BISHOP BERLE

H. BIRKHAUSER (Basel) AND H. BLOCH (New York), Editors: *Advances in Tuberculosis Research. Pp. 307, S. Karger, Basel and New York, 1950, Price 38 Swiss francs or about $9.00.*

This book of reviews is a special issue of the *Bibliotheca Tuberculosea* and represents a supplement to the *Schweizerische Zeitschrift fur Tuberculose.*

Progress in research in tuberculosis has been vastly accelerated in recent years due to the introduction of chemotherapy and a new approach to the bacterium

itself. The latter approach was initiated by Dubos, whose work on chemotherapy of diseases caused by gram-positive bacteria undoubtedly influenced, albeit indirectly, research in the chemotherapy of tuberculosis. This approach is aimed at the fundamental aspects of bacterial growth, morphology, virulence, and rapid cultural diagnosis. It is fortunate that in tuberculosis, unlike the situation in diseases caused by pneumococci and *Streptococci*, the partial success of chemotherapy stimulated more research in fundamental problems. The rapid progress of research calls for reviews, particularly since the freshly obtained results seem to be pregnant with new implications. Thus, the moment is suitable for reviews rather than for monographs.

The reviewers are all active contributors to the literature in their respective fields. The first chapter by Seibert on the "chemistry of tuberculin" deals concisely with that subject and also with some of the immunological aspects of this problem. The second chapter by Canetti and Rocher of the Pasteur Institute of Paris discusses the resistance of the tubercle bacillus to streptomycin. The reading of this well-organized review is facilitated by graphs and 9 tables. The third chapter on recent advances of surgery of pulmonary tuberculosis by H. Good emphasizes the indications for the choice of therapy as well as the results of surgical intervention, and deals with the ventilation of the blood from the standpoint of the thoracic surgeon. Because of what it offers, and by avoiding the descriptions of surgical technique, the chapter should be interesting to the nonsurgical readers. The stimulating chapter by Middlebrook on bacteriologic research, consisting of 20 pages and about 100 references, seems to be all too short for the subject. The discussion includes bacterial metabolism, morphology, virulence, the toxic effect of tubercle bacilli, the experimental disease, bacteriologic and serologic diagnosis. Middlebrook and one of the editors (H. Bloch) made significant contributions to this field. Diehl's chapter on heredity in tuberculosis is interesting. He is one of the authors of a monograph on tuberculosis in twins (K. Diehl and O. von Verschner, Zwilingstuberculose, Fischer, Jena, 1933). Their spectacular findings in identical twins attracted a great deal of attention. Diehl's review covers his own and Lurie's well-known experimental studies on the influence of heredity on tuberculosis. The next chapter by Canetti deals with tuberculin sensitivity during latent infection, and is especially timely because of the changing epidemiology of the disease. Canetti's recent book, *L'Allergie tuberculeuse chez l'homme*, 1946, Flammarion, Paris, made him a good selection for this thoroughly and clearly written chapter. Suter writes on the chemotherapy of tuberculosis both from the experimental and clinical standpoint with a section on *in vivo* and *in vitro* methods. His chapter covers 74 pages and has 656 references. It is a most comprehensive and painstaking review which might be incorporated later into a monograph.

Two of the reviews are written in English, the others in French and German. Their style is clear and simple. Due to the well-selected topics and the quality of the reviews, this volume should find a large number of readers among students of clinical and experimental tuberculosis.

J. Freund

THE AMERICAN REVIEW OF TUBERCULOSIS
ABSTRACTS

Edited by LAWRENCE B. HOBSON

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CLINICAL STUDIES, TUBERCULOSIS

Pregnancy and Tuberculosis.—Observations were made during 718 pregnancies in 534 different tuberculous patients. In quiescent tuberculosis, pregnancy causes little additional risk to which the patient is not already subject. The 2 most dangerous periods are the first four months and the time immediately after parturition. In cases of active tuberculosis, there is a better prognosis with spontaneous abortion than with full-term pregnancy. The author theorizes that chorionic gonadotropin is potentially adverse to tuberculosis while estrogens are favorable. If this is correct, then there is very little advantage in interrupting pregnancy after the first trimester. Also, care must be observed in the use of gonadotropic substances in tuberculous cases. Observations were made in 240 pregnancies in 169 patients with quiescent tuberculosis. There was a ten-year survival rate of 86 per cent. Recrudescence occurred in 10 cases during pregnancy and in 20 within a year after delivery. In active tuberculosis, the survival rate depended upon when the disease was discovered; the later the detection the worse the prognosis.—*Pregnancy and tuberculosis, H. M. Turner, Lancet, April 15, 1950, 1: 697.*—(*A. G. Cohen*)

Cavity Closure by Emphysema.—A case of coexisting giant bulla and tuberculous cavity in the same portion of the lung is described. This is the second reported case in which a giant bulla acted much the same as an artificial pneumothorax in producing closure of a tuberculous cavity. It is postulated that the bronchioli are narrowed as a result of the involvement of tuberculosis. By the development of a check-valve mechanism, the trapped air produces a giant bulla which is thought to be under considerable pressure. It is known that giant bullae may attain positive pressures as high as plus 11 cm. of water. If this is fortuitously placed in relationship to a segment of lung containing a tuberculous cavity it is able to exert its pressure effect maximally upon the segment; its ultimate effect is considered to be that of a positive pressure pneumothorax. Emphysematous bullae under these circumstances are known to remain unchanged or show insignificant changes in size and shape over long periods of time. This opinion is confirmed by the present case in which relatively little alteration occurred in the size of the bulla over a period of 22 years.—*Giant bullous emphysema producing closure of a tuberculous cavity, M. M. Leder & D. W. Zahn, Am. J. Roentgenol., April, 1950, 63: 498.*—(*T. H. Noehren*)

Relapse after Artificial Pneumothorax.—The incidence of relapse with fluid or spread is high in patients with inadequate pneumothoraces; the reasons therefor are evident. The current investigation deals with relapses occurring in 58 patients with perfectly free pneumothoraces and unilateral disease. In 41, there was fluid; in 7, fluid and spread; and in 10, spread alone. In all but 3, there was atelectasis of a lung, lobe, or segment. In some cases, the atelectasis was transient and the presence of fluid fluctuated correspondingly. The longer the period of bed rest prior to pneumothorax, the shorter the duration of atelectasis. There was no significance in the interval between induction of pneumothorax

and section of adhesions. In many cases, atelectasis appeared long after pneumonolysis. Relapse appeared anywhere from a few days to several years after atelectasis. Atelectasis in tuberculosis varies in its sequelae according to the degree of entrapment of virulent organisms. Gradual fibrosis and gross tissue damage may be the only effects. On the other hand, an acute pyogenic abscess may develop, or the affected lung may become the site of a tuberculous abscess. With pneumothorax, the possibilities of fluid accumulation are great.—*An investigation into the factors contributing to relapse in cases of pulmonary tuberculosis treated by unilateral artificial pneumothorax, G. P. Maher-Loughnan, Tubercle, April and May, 1949, 31: 74 and 98.*—(*A. G. Cohen*)

Pneumoperitoneum for Tuberculosis.—A patient was receiving both pneumoperitoneum and right pneumothorax for tuberculosis. One week after a refill of each space, the pneumoperitoneum disappeared while the pneumothorax became very extensive with positive pressures. A leak between the two spaces was postulated.—*Leakage of air from pneumoperitoneum into pleural cavity, E. W. Street, Lancet, April 8, 1950, 1: 669.*—(*A. G. Cohen*)

Post-tuberculous Bronchial Lesions.—The author reports 60 cases of obstruction of the middle lobe bronchus or secondary bronchiectasis due to active or old tuberculous lymphadenitis. In early tuberculosis there may be pressure of caseous nodes on the bronchi. This may cause obstruction for many months. The obstruction may resolve but leave residual lung changes such as bronchiectasis. The node may perforate with or without the expectoration of broncholiths, or there may be a residual fibrous stricture of the bronchus. In all of these situations, the original offending gland calcifies. Any bronchus may be affected. The smaller ones are more vulnerable, particularly that of the middle lobe. Of 93 cases of post-tuberculous bronchostenosis or bronchiectasis, 60 involved the middle lobe. In several cases, some segments of other lobes also were involved, particularly the cardiac and anterior (pectoral) segments of the upper lobe. The bronchi also are vulnerable to the effects of nontuberculous adenitis and malignant lesions. The entire middle lobe was affected in 50 cases, its lateral division in 9, and medial in one. Only 5 were in children below the age of twelve years; 41 were in adults thirty to seventy-two years old. In cases of subsided bronchostenosis, although the lumen has been restored, secondary fibrosis and bronchiectasis may persist. Strictures may be partial or complete and usually are located 1 to 1.5 cm. from the orifice. If the lateral division is involved, the stenosis is located at the very origin. Calcification may be of radiographic interest only or may produce symptoms such as expectoration of broncholiths or of inflammation. They often cause technical operative complications. The lobe may be consolidated by pneumonitis, shrunken and airless, honey-combed, or contain cystic spaces with or without infection. The clinical picture varies greatly. The greatest incidence is in the fifth decade of life. Presenting symptoms are (*1*) those of bronchiectasis, (*2*) hemoptysis, (*3*) general weakness, (*4*) single attack of pneumonia, (*5*) lung abscess or suppurative pneumonia, (*6*) empyema, (*7*) recurrent fever, or (*8*) those simulating carcinoma. The therapy in many cases is conservative. Resection is indicated if there is broncholithiasis, bronchial obstruction, or chronic abscess formation. Bronchiectasis with minimal symptoms is per se no strong indication for resection. The operation may be difficult and the lower lobe may have to be sacrificed. In this series, operation was performed for 17 patients with one pending, making a total of 30 per cent.—*Post-tuberculous bronchostenosis and bronchiectasis of the middle lobe, R. C. Brock, Thorax, March, 1950, 5: 5.*—(*A. G. Cohen*)

Vitamin D for Skin Tuberculosis.—There is evidence that in the pathogenesis of skin tuberculosis there exist factors other than the virulence of the tubercle bacilli and the allergic condition of the host. Factors such as disturbances in the peripheral circulation, acro-

asphyxia, chilblains, radiodermatitis, and scars may diminish resistance locally favoring the localization of tubercle bacilli. The mode of action of vitamin D therapy and of salt-free diets in the treatment of skin tuberculosis shows remarkable similarities. These can be explained by the fact that both forms of treatment are directed towards changes in the metabolism in the skin. The effect of vitamin D therapy seems to be more intensive than that of a salt-free diet. One result is an increase in the mineral content of the skin; there is an increase in calcium and a diminution in the base content. High dosage of vitamin D apparently increases the excretion of chlorides in the urine. The chloride level in the serum is constant in many cases treated with a salt-free diet. In contrast, the serum chloride level shows a statistically significant diminution in individuals treated with vitamin D. Experimental and clinical studies seem to indicate that vitamin D acts through metabolic changes in the skin rather than through a chemotherapeutic effect. This would explain the favorable effect of the therapy in skin tuberculosis and its failure in pulmonary tuberculosis. By combining vitamin D therapy and a salt-free diet, it is to be expected that equally good therapeutic effects can be obtained with a lower dosage of vitamin D.—*Ueber den Wirkungsmechanismus der Vitamin-D-Therapie bei Hauttuberkulose, R. Brett & K. H. Eckes, Deutsche med. Wchnschr., July 15, 1949, 74: 2728.*—(*L. Molnar*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Beryllium Granulomatosis.—A review of the current data of chronic pulmonary granulomatosis in beryllium workers indicates that proof that beryllium is the sole etiologic agent involved is still incomplete. The so-called "neighborhood cases" indicate that there is no good correlation between the degree, type or duration of exposure, and the development of disease. Clinically, the latent period between the time of exposure and the onset of illness is extraordinarily inconstant and may vary from a few months to more than five years. In all except the occasional mild and asymptomatic cases dyspnea was a constant complaint. It is usually accompanied by cough, anorexia, weight loss, and easy fatigability, and occasionally by fever to 103° or 104° F. Except for cyanosis and scattered rales, physical findings are not striking. Polycythemia is usually present in all except the mildest cases and a moderate eosinophilia without an accompanying leukocytosis is common. The roentgenographic manifestations are extremely protean, but an attempt at classification includes 3 types: (*1*) granular, (*2*) reticular, and (*3*) nodular. In all 3 the involvement is diffuse, though not necessarily uniform, throughout both lungs. Acute respiratory infections are the most common complications of chronic pulmonary granulomatosis. Symptomatically they exert a temporarily deleterious effect but, following recovery, the patients revert to their status prior to the attack. One patient in the author's series developed a complicating tuberculous infection; but neither disease process appeared to exert an untoward effect upon the other in spite of 2 episodes of right-sided spontaneous pneumothorax. There is some indication that the types now recognized are all late manifestations, and that prior to the development of chronic pulmonary granulomatosis there may be a preliminary and perhaps transitory phase, comparable to the acute form, but so mild in degree that it escapes recognition. Differential diagnosis should be carefully considered in each case to rule out the possibilities of sarcoidosis, the various inflammatory infections, silicosis, and cardiovascular diseases.—*A consideration of the roentgen diagnosis of chronic pulmonary granulomatosis of beryllium workers, A. G. Robert, Am. J. Roentgenol., April, 1950, 63: 467.*—(*T. H. Noehren*)

Talc Pneumoconiosis.—Four cases are reported as examples of talc pneumoconiosis with an additional case of concurrent pulmonary neoplasm. The principal clinical indications of talc pneumoconiosis are dyspnea, cough, cyanosis, clubbed fingers, and dimin-

ished vital capacity. The specific relation to asbestosis is remarkable when the clinical picture is correlated with roentgen findings. The early roentgenographic manifestation in either disease is haziness of the lung field with fine reticulation or soft nodulation which may be so delicate as to escape detection. It is quite unlike the distinct nodulation typical of silicosis. As the disease progresses, the parenchymal pulmonary lesions gradually become denser and tend to become confluent, developing asymmetrically with compensatory emphysema, without nodulation and with a predilection for pleural involvement. Clinical indications of unfavorable prognosis, such as anorexia and weight loss, have been noted in both talc and asbestosis pneumoconiosis. Because limitation of respiratory motion is often more informative than the chest film or even a series of chest films, roentgenoscopy is of value. There is a possibility that early disease processes will become arrested but they are apt to become progressive as a result of infection. There is no recovery from established disability.—*A type of pneumoconiosis, A. A. Hobbs, Jr., Am. J. Roentgenol., April, 1950, 63: 488.*—(*T. H. Noehren*)

Parasitic Calcification.—Calcification may occur in a large number of parasites. Its appearance generally indicates death of the parasite or the intermediate cyst stage. It tends to follow accurately the outlines of the dead worm, and a knowledge of the shape of the worm will enable the correct diagnosis to be made. Parasitic calcification tends to be amorphous and it may cause difficulties in the differential diagnosis of ectopic calcification. On rare occasions Guinea worms may occupy the subcutaneous tissues of the overlying chest wall. Such ectopic calcification in chest roentgenograms may lead to the mistaken diagnosis of intrapulmonary calcified tuberculous lesions. Close inspection of the lesion will, however, reveal that the calcified mass has the characteristic coiled linear appearance of a worm, while a tangential view of the chest wall will reveal the calcification to lie in the thoracic wall.—*Roentgenology of parasitic calcification, E. Samuel, Am. J. Roentgenol., April, 1950, 63: 512.*—(*T. H. Noehren*)

Carcinoma of the Lung.—A case of carcinoma of the lung is presented in which both the operative and gross autopsy diagnoses were mesothelioma of the pleura. Multiple microscopic sections from approximately 40 different areas finally demonstrated a small lesion in a minor bronchiole which was identical with the other neoplastic tissue; this was regarded as the primary lesion. If this case was mesothelioma, it presents the problem of whether mesothelioma can metastasize to the lungs. The demonstration of one lesion in one bronchiole which is identical with the neoplastic tissue elsewhere and the demonstration of neoplasm in the mediastinal lymph nodes, pleura, bone, and brain lead to the conclusion that this was a primary neoplasm of the lung.—*Carcinoma of lung: Report of a case simulating pleural mesothelioma, L. W. Fix, U. S. Armed Forces M. J., March, 1950, 1: 269.*—(*T. H. Noehren*)

Gastric Symptoms in Bronchogenic Carcinoma.—Of 225 patients with bronchogenic carcinoma, 72 had symptoms referable to the stomach. Four types of symptoms can be distinguished: (*1*) decrease of appetite, which was found in 26 of the 72 patients. (*2*) Eighteen patients complained of loss of appetite, pressure of pain in the gastric region, eructation, sensation of fullness, nausea, and vomiting. In all of these cases there were large lymph node metastases near the trachea or in the region of the bifurcation extending into the posterior mediastinum. Roentgenologically there was an increase or decrease of gastric tonus and peristalsis, due to irritation or interruption of the vagus. (*3*) In 15 cases there was a stomach or duodenal ulcer; all of these patients had metastases to the mediastinum. (*4*) Postoperative symptoms referable to the stomach are caused by change in shape or position of the stomach.—*Magenbeschwerden als Fernsymptom bei Bronchuskarzinom, M.*

Wezel, Wien. klin. Wchnschr., April 14, 1950, 62: 261.—(G. C. Leiner)

Supradiaphragmatic Thoracic Duct Cyst.—This is the report of a case of a young woman with a posterior mediastinal mass which pushed the esophagus forward and produced atelectasis of the right lower lobe. At operation, a cystic mass was revealed; this contained milky fluid. At its upper pole, there was a duct which did not lead to the venous system. At its lower pole, a duct arose from below the diaphragm. Both ducts were ligated and the mass resected. Thoracic duct cysts are not rare below the diaphragm. Only 7 cases in which the cysts were located supradiaphragmatically have been reported previously.—*Supradiaphragmatic thoracic duct cyst, G. L. Emerson, New England J. Med., April 13, 1950, 242: 575.—(A. G. Cohen)*

Treatment of Cystic Hygroma.—It is suggested that roentgen therapy should be given the first consideration in the treatment of cystic hygroma. If for any reason operation seems advisable, the amount of treatment estimated to be necessary should not interfere with any operative procedures that seem advisable. Operation when the mediastinum is involved should not be considered. This is indicated by Figi's experience at the Mayo Clinic where only one of 13 cases was considered suitable for operation. The experience on the part of Figi, Portmann, Hodges *et al.*, as well as the experience of the authors, seems to indicate the line of treatment in this rare condition (Authors' summary).—*Cystic hygroma of the neck and mediastinum successfully treated by roentgen rays, G. E. Pfahler & H. H. Perlman, Am. J. Roentgenol., April, 1950, 63: 539.—(T. H. Noehren)*

Pleural Mesothelioma.—The roentgenographic diagnosis of pleural mesothelioma as previously reported has emphasized the findings of pleural effusion, usually massive, with or without tumor nodules. A case is presented in which the roentgenograms show only gross pleural thickening without evidence of effusion or pleural or parenchymal tumor nodules. The fusion of the visceral and parietal pleurae by tumor tissue explained the absence of the pleural effusion which is usually observed. Careful exploration of the bronchial tree at autopsy failed to disclose an intrabronchial tumor.—*Roentgen diagnosis of pleural mesothelioma (endothelioma), H. Schwartz, Am. J. Roentgenol., April, 1950, 63: 530.—(T. H. Noehren)*

ANTIMICROBIAL THERAPY

Streptomycin for Tuberculous Meningitis.—There is clinical evidence, confirmed by postmortem examination, that tuberculous lesions may be present in the meninges long before the clinical symptoms of meningitis are manifest. A painstaking search may reveal the presence of chemical changes and of tubercle bacilli in the spinal fluid in the earliest stages of the disease. Routine spinal taps every fifteen to twenty days are recommended for patients already hospitalized for miliary tuberculosis, and for infants with primary tuberculosis; when abnormalities are found, intrathecal and intramuscular administration of streptomycin must be started immediately. The duration of the treatment in 60 cases of tuberculous meningitis treated with streptomycin in a special ward was generally about three months. One milligram per kg. of body weight was used intrathecally, that is, about 10 mg. in infants and 20 to 30 mg. in older children, in 2 to 3 cc. of physiological saline solution. The course of intrathecal treatment consisted of 15 daily injections, 15 on alternate days, then an injection twice a week for two weeks and one a week for one month. When the treatment was effective, the spinal fluid changes gradually disappeared after the treatment was discontinued. If these changes persisted for two months, the treatment was resumed. The intrathecal treatment was combined with intramuscular administration of the drug at a dosage of 40 mg. per kg. of body weight. Three months after the treatment was discontinued 33 patients were alive out of the total of 60

treated; of these, 19 were in good general condition without clinical manifestations of illness. In 6 of these patients there were no spinal fluid changes; in 6 there were distinct abnormalities; and in 7, marked changes in the spinal fluid. Nine of the survivors showed manifest symptoms and signs of meningitis. All of these cases had, after the beginning of the treatment, an initial phase of improvement followed by relapse. Another group of 5 survivors showed no improvement under streptomycin treatment. In these cases the drug probably prolonged life. Of the 27 patients who were treated with streptomycin and died, 12 had a fatal course without any improvement, in 4 there was a slight improvement, and in 7 there was considerable improvement at the beginning of the treatment, followed by a relapse which led to death. Of 14 infants under two years of age, 12 rapidly deteriorated and died. This high mortality rate in infants may be due to limited powers of defense in this age group and possibly also to the fact that the course of the disease is more rapid. Cases with only meningeal involvement responded better to treatment than those with brain involvement. The latter cases were complicated by hydrocephalus, hemiplegia, monoplegia, pyramidal and extrapyramidal manifestations due to vascular lesions with consequent softening of cerebral areas. Relapses occurring in the course of treatment with streptomycin usually indicate a bad prognosis. When the relapse occurs after the treatment has been suspended, the resumption of the treament has more chance of being effective. The type and frequency of toxic effects were in line with those noted by other observers.—*Meningitis tuberculosa infantil y estreptomicina—Estudio de 60 casos, R. Garcia Alonso, J. Villota, L. Burgoa, & J. Vanaclocha, Rev. espan. de tuberc., February, 1949, No. 167: 69.*—(*L. Molnar*)

Streptomycin in Tuberculous Meningitis.—A three-months' follow-up study was made in 60 cases of tuberculous meningitis treated with streptomycin and reported in a previous paper. Eleven more deaths raised the total of fatal cases to 38. The deaths occurred in patients with long clinical course and in those whose condition was very grave on admission. Of the 22 patients still alive after this further three-month period, 20 are free of clinical symptoms.—*Meningitis tuberculosa infantil y estreptomicina—Estudio de 60 casos, R. Garcia Alonso, J. Villota, L. Burgoa & J. Vanaclocha, Rev. espan. de tuberc., March, 1949, No. 167: 197.*—(*L. Molnar*)

Intracisternal Use of Streptomycin.—In 2 patients with tuberculous meningitis the administration of streptomycin into the lumbar sac was technically difficult and the drug was, therefore, administered intracisternally. In one patient there was respiratory failure leading to death, and in the other coma was followed by a pronounced change in mental status for several days. These reactions are believed to have been due to a direct neurotoxic action of streptomycin on the medullary centers and cerebral cortex rather than to trauma or disease.—*Reactions following intracisternal use of streptomycin, F. E. G. Valergakis, D. S. Hays, & A. M. Sutherland, J.A.M.A., March 11, 1950, 142: 720.*—(*H. Abeles*)

Tuberculous Peritonitis. — Twenty - six patients with tuberculous peritonitis were treated with streptomycin. Twenty-five of the 26 patients responded favorably to streptomycin therapy. One patient with coexisting pulmonary tuberculosis failed to respond and died. Four of the improved patients had a relapse. Two of them responded to a second course of streptomycin, one failed to respond. One patient was not re-treated and died following a relapse. A majority of the patients had been seriously ill and many were chronically ill. The uniformity and rapidity of response, the subsidence of fever and abdominal symptoms, the general improvement, the striking gross objective improvement observed in 3 follow-up laparotomies, and the fact that 6 patients have returned to work are clear indications of the effect of the drug. In most instances streptomycin therapy changed the trend of the disease and shortened the disease

process. The duration and type of peritoneal involvement did not influence demonstrably the response to therapy. Tuberculosis of the peritoneum responded as well as, or better than, coexisting tuberculous lesions elsewhere. Streptomycin did not prevent the development of new lesions. Comparable results were obtained with daily administration of 1 or 2 gm. of the antibiotic. The smallest amount of streptomycin needed for the arrest of the disease is yet to be determined. Although immediate improvement following streptomycin therapy was excellent in most cases, continued observations will be necessary to determine the efficacy of streptomycin in the ultimate control of the disease. The development of new extraperitoneal lesions during and after therapy and the persistence of histologic evidence of tuberculosis in 2 cases make the prognosis extremely guarded (Authors' summary).—*Tuberculous peritonitis treated with streptomycin, R. H. Wichelhausen & T. M. Brown, Am. J. Med., April, 1950, 8: 421.—(T. H. Noehren)*

Tuberculous Lymphadenitis.—The use of streptomycin in 7 cases of tuberculous lymphadenitis gave a poor immediate result in one, a good one in 6. In 2 the drug was unquestionably of great value, regardless of the eventual outcome, since in one it obviated surgery for intestinal obstruction and in the other prepared the patient for operation for coincident thyrotoxicosis. On the other hand, in 2 in whom a follow-up of one year was possible, relapse occurred. In the 2 patients who relapsed, the recurrent lymphadenopathy subsided over a period of months under treatment with rest and heliotherapy. Since recovery was not uncommon in the prestreptomycin era with these simple measures, there is reason to doubt the desirability of using this drug in the ordinary case of scrofula, the more so since the tubercle bacillus is likely to become resistant to streptomycin and it may later be ineffective when more urgently needed by the patient.—*Streptomycin in the treatment of tuberculous lymphadenitis, J. A. C. Gray, U. S. Armed Forces M. J., April, 1950, 1: 476.—(T. H. Noehren)*

Gynecologic Tuberculosis.—Sixteen patients with genitoperitoneal tuberculosis were treated with streptomycin for six to eight weeks prior to operative intervention and for three weeks after the operation. Whenever possible, total hysterectomy with bilateral salpingo-oophorectomy was performed. All patients showed improvement during the preoperative period. The preoperative antibiotic therapy seemed to make the technical difficulties encountered in surgical treatment of genital tuberculosis much less formidable.—*Streptomycin in gynecologic tuberculosis, a preliminary report, H. Sered, F. H. Falls, & B. P. Zummo, J.A.M.A., February 25, 1950, 142: 547.—(H. Abeles)*

Tuberculous Tenosynovitis.—Two cases of histologically proved tuberculous tenosynovitis are reported. Both patients responded promptly to treatment with streptomycin, 0.5 gm. daily for six weeks. One patient had a recurrence after a year and again responded to streptomycin treatment. Immobilization was not used in treating either of these patients.—*Streptomycin in the treatment of tuberculous tenosynovitis, J. M. Miller, R. J. Lipin, & M. Ginsberg, J.A.M.A., February 11, 1950, 142: 408.—(H. Abeles)*

Clinical Tests in Chemotherapy.—Over 200 cases of pulmonary tuberculosis have been treated at the St. Göran Hospital in Stockholm was PAS and Diasone and, since January 1947, with PAS and streptomycin. Results were evaluated by temperature records and blood examinations which included studies of the Arneth-Schilling formula and the sedimentation rate. Variations in body temperature and blood reactions develop independently. The Arneth-Schilling reaction is apparently somewhat more markedly influenced by streptomycin than by PAS. After PAS is added, an improvement of the sedimentation rate is often noted. If the sedimentation rate and the leukocyte picture grow worse, de-

velopment of drug resistance, especially to streptomycin, may be inferred.—*Sur l'appréciation des résultats de la chimiothérapie de la tuberculose pulmonaire, A. Westergren, Poumon, May-June, 1949, 5: 187.*—(*A. T. Laird*)

PAS for Tuberculosis.—Experience with intensive, careful treatment of pulmonary and extrapulmonary tuberculosis has convinced the authors that *p*-aminosalicylic acid (PAS) is a better "basic" form of therapy for serious tuberculosis than streptomycin alone or in combination with PAS. It seems the best treatment for mild or moderately severe cases. Where adequate pretreatment observations could be made, it was found that of 61 patients treated for pulmonary tuberculosis 28 were considerably improved, 24 moderately so, and only 9 were unchanged or worse. The sputum became negative for tubercle bacilli in 31 of 44 previously positive cases; among the patients who remained positive, 3 showed disappearance of their cavities on conventional films and planigrams. Improvement in the sedimentation time and increase in the blood lymphocytes were noted in all patients who improved clinically. Toxic symptoms disappeared more slowly than with streptomycin treatment, usually persisting about four weeks. Exudative processes responded most favorably; miliary disease was not easily affected although PAS by continuous intravenous drip should be the treatment of choice in cases of miliary tuberculosis due to streptomycin-resistant bacilli. A good effect on residual cavities following thoracoplasty and on tension cavities was demonstrated. The response of bronchial tuberculosis was uniformly good with slower healing than with streptomycin or TB 1/698; the end result was often more favorable because of the absence of marked fibrous stenosis. In urogenital tuberculosis PAS is not the drug of choice although alleviation of the symptoms of tuberculous cystitis was seen. Experience with bone and joint tuberculosis is too meager to warrant conclusions although it seems likely that PAS is beneficial. PAS is highly recommended for the treatment of tuberculous empyema complicating intra- or extra-pleural pneumothorax, and also of acute exudative pleuritis. The intrapleural injection of PAS in doses of 1 to 2 gm. for pleuritis, and of 2 to 4 gm. for empyema has been recommended. It is essential that the plural space be aspirated as completely as possible prior to instillation; irrigation of the space with 2 to 4 per cent PAS solution to which heparin has been added should precede the instillation. The results in tuberculous empyema have been gratifying and the only resistant cases have been those with large bronchopleural fistulae. PAS is recommended prior to pneumothorax in preference to streptomycin; but before major surgery streptomycin alone or with PAS is the treatment of choice. The authors condemn the routine use of a combination of drugs since there is no convincing evidence of potentiation. The emergence of resistance to streptomycin is not delayed but obscured by combination treatment. The use of streptomycin should be restricted to critical situations; even severe exudative cases should be treated with a preliminary course of PAS. If such a regimen is carried out, streptomycin treatment can be limited to several short courses of 30 gm. each. Resistance to PAS is difficult to demonstrate because tubercle bacilli from PAS-treated patients often fail to grow even in media without PAS. This is temporary, and clinically it is quite certain that PAS resistance develops, usually during the initial three to six months of treatment. The PAS granules or dragees used were well tolerated by all patients.—*Erfahrungen mit der Paraaminosalicylsaure (PAS)—Therapie der Tuberkulose, St. J. Leitner & P. Masson, Schweiz. med. Wchnschr., April 15, 1950, 80: 375.*—(*H. Marcus*)

PAS, Streptomycin, and Surgery.—Cases of pulmonary tuberculosis treated surgically were classified as typical or borderline according to suitability. The borderline cases received either *p*-aminosalicylic acid (PAS) for 85 days or streptomycin for 44 days. The drug was continued throughout the operation and for about one month thereafter. The typical cases received PAS, streptomycin, or no chemo-

therapy. Where a drug was used, it was given for one week before operation and two weeks afterward. In the borderline cases, the effect of PAS and streptomycin preoperatively was similar, except that the action of streptomycin was more rapid. The cases in this group were converted by treatment into as good operative subjects as the typical cases. There were less postoperative spreads in the borderline cases. This was interpreted as due to the more prolonged preoperative therapy. It is concluded that borderline cases can be converted into good risks with preoperative chemotherapy. PAS is the drug of choice with streptomycin held in reserve for postoperative complications.—*Para-aminosalicylic acid (PAS) and streptomycin in the surgical treatment of pulmonary tuberculosis, G. Birath, T. Bruce, C. Crafoord, & L. G. Uggla, Thorax, March, 1950, 5: 59.*—(*A. G. Cohen*)

Action of Streptomycin.—The present report deals with the influence of streptomycin on bacterial oxidation of fatty acids. Washed 7-day-old cultures of streptomycin-sensitive and -resistant strains of avian tubercle bacilli were exposed at pH 7 to streptomycin, 33 γ per ml., in a manometric apparatus containing air. After thirty minutes, a fatty acid substrate was added and the course of oxidation observed. The effect of streptomycin on the oxidation of stearic acid by sensitive and resistant cultures of the "Gratia" strain of *E. coli* also was studied. Although the site of action of streptomycin was not clearly defined, the sensitive mechanism appeared to be the oxidation of the breakdown products from the fatty acids rather than the oxidation of the chain itself. The resistant avian tubercle bacilli oxidized the fatty acids without streptomycin inhibition. Although *E. coli* oxidized the stearate somewhat differently, a similar inhibition by the drug was observed. Streptomycin-resistant *E. coli* had lost the major portion of the oxidative mechanism for higher fatty acids.—*The action of streptomycin. IV. Fatty acid oxidation by Mycobacterium tuberculosis, avian type, E. L. Oginsky, P. H. Smith, & M. Solotorovsky, J. Bact., January, 1950 59: 29.*—(*F. G. Petrick*)

Streptomycin and Tubercle Bacilli.—Tubercle bacilli were isolated and their sensitivity to streptomycin determined while 2 groups of patients were treated daily with streptomycin, 1 gm. and 1.8 gm., respectively. Drug-resistant cultures began to appear in the fourth week of treatment. Usually a resistance increased rapidly once it was established. Patients with highly positive sputum were more prone to yield drug-resistant strains during streptomycin treatment than those with fewer organisms. The resistance of the bacilli seemed to be a permanent characteristic. Animals infected with highly resistant organisms did not respond adequately to treatment with streptomycin. In guinea pigs infected with artificial mixtures of sensitive and resistant organisms, the *in vivo* resistance depends upon the relative number of drug-resistant organisms. Tubercle bacilli recovered from the animals after streptomycin therapy showed essentially the same *in vitro* sensitivity as the original culture used to infect them. In experimental tuberculosis in guinea pigs, streptomycin therapy seemed to manifest its efficiency only after hypersensitivity and acquired resistance had developed. Tuberculosis of guinea pigs infected intracerebrally with a virulent strain of bacilli could be controlled by very large doses of streptomycin intramuscularly.—*La streptomycine et le bacille tuberculeux, W. Steenken, Jr., E. Wolinsky, A. Reginster & P. Pratt, Revue Belge de Pathologie et de Médicine Expérimentale, September, 1949, 19: 225.*—(*A. T. Laird*)

Usnic Acid with Streptomycin.—It has been shown previously that usnic acid has a marked *in vitro* antibacterial action on the tubercle bacillus. In this study 5 groups of 20 guinea pigs each were inoculated with tubercle bacilli (H37Rv) and managed as follows: (*1*) untreated; (*2*) only usnic acid, 20 mg. in oil-Tween 80 subcutaneously for six days, then 10 mg. per day for 24 days; (*3*) large doses of streptomycin, 6 mg. per day for 30 days; (*4*)

small doses of streptomycin, 2 mg. per day for 30 days; (5) usnic acid plus small doses of streptomycin. Unexpectedly none of the animals died of tuberculosis even in the untreated control group. Comparison of the severity of the disease among the various groups showed that usnic acid or low doses of streptomycin alone showed no retardation of the disease. The results with a combination of usnic acid and small doses of streptomycin were similar to those with large doses of streptomycin. It is thought that these results with usnic acid and streptomycin may be compared to the combined action of streptomycin and *p*-aminosalicylic acid, resulting in a potentiation of the effect of streptomycin, thus making the use of smaller doses possible with fewer toxic symptoms.—*Streptomycin and usnic acid in guinea pig tuberculosis, A. Marshak & M. Kuschner, Pub. Health Rep., February 3, 1950, 65: 131.*—(*S. Hadley*)

Resistance to Antibiotics.—Studies have shown that the manner in which bacteria become resistant to penicillin and streptomycin is different. In both the process is stepwise. In the case of penicillin as studied with *Staphylococcus aureus*, the first-step mutants have a very uniform degree of resistance and are only slightly more resistant than the original strain. From these mutants more resistance strains may be obtained by successive small steps. The mutation occurs only once in every 10^9 bacteria per generation, so that the possibility of a double mutant is small. With streptomycin however there is a great variation in the first-step mutation from low to very high resistance so that an extremely resistant population may arise in a relatively short time. Studies with aureomycin indicate that the pattern of mutation probably is similar to that with penicillin. These studies are complicated however by a loss of potency of the drug during the experiments. From such experiments we find an answer to some of the problems that arise in treatment of bacterial infections with various antibiotics.—*Patterns of bacterial resistance to penicillin, aureomycin, and streptomycin, M. Demerec, J. Clin. Investigation, September, 1949, 28: 891.*—(*S. Hadley*)

Comparative Antimicrobial Therapy.—Guinea pigs experimentally infected with tuberculosis were treated with comparable courses of streptomycin alone, streptomycin combined with *p*-aminosalicylic acid (PAS), streptomycin combined with TB 1/698, PAS alone, TB 1/698 alone, and 2 new compounds chemically related to PAS. The human strain H37Rv was used and inoculations were made into the inguinal region. The effectiveness of treatment was evaluated by the amount of tuberculous disease found at autopsy in the liver, spleen, lymph nodes, and lungs. The dosage of all drugs was standardized in relation to the dosage commonly employed in clinical tuberculosis by giving twice the usual clinical dose of drug on a body-weight basis. The results indicate that the 2 new drugs which showed considerable promise *in vitro* were ineffective *in vivo*. TB 1/698 by itself was considerably less effective than PAS alone, and in combination with streptomycin TB 1/698 gave less favorable results than streptomycin therapy alone. By all odds the most favorable combination was that of streptomycin and PAS. In all animals treated with this last combination the severity of the disease as determined at autopsy was only 0.7 as contrasted to a maximal possible rating of 20. This compared with a rating of 13.6 in untreated controls, a rating of 9.6 with TB 1/698, and a rating of 3.1 with PAS. It should be pointed out that Domagk has used considerably larger doses of TB 1/698 in his experimental animals, but because of the known toxic propensities of the drug it seemed wise to use only twice the human dose.—*Vergleich der Kombinations—therapie von Streptomycin mit TB1 (Thiosemicarbazon) oder PAS (Para-aminosalicylsaure) sowie zwei neuen PAS-Derivaten bei der Exzperimentellen Tuberkulose, S. Moeschlin & B. Dimiral, Schweiz. med. Wchnschr., April 15, 1950, 80: 373.*—(*H. Marcus*)

Anemia with TB 1/698 Therapy.—Anemia occurred in about one-half of the cases of

tuberculosis treated with TB 1/698, 0.4 gm. a day. The lower dosage of 0.2 gm. a day now in use produces a considerably lower incidence and gravity of anemia. In such anemias hemoglobin and red cells are uniformly reduced so that the color index remains around 1.0. The level of the indirect bilirubin in the serum is increased; in the urine there is urobilin and increased quantities of urobilinogen. The anemia appears as a hemolytic crisis, also demonstrated by the increased activity of the bone marrow. When the administration of the drug is continued in smaller doses in spite of the complication, the rate of reticulocytes increases as the symptoms subside. One death has been caused by the drug. A simple toxic effect of the drug is unlikely. Toxic products liberated by the destruction of tubercle bacilli as an effect of the chemotherapeutic agent might be a cause for this anemia. TB 1/698 may act as a haptene and the hemolytic crisis be brought about by an antigen-antibody reaction. In view of the possible toxic complications, treatment with TB 1/698 should only be carried out under institutional care.—*Zur Frage der Anaemie bei Behandlung mit TbI/698, W. Pribilla & E. D. Koester, Deutsche med. Wchnschr., June 24, 1949, 74: 795.*—(*L. Molnar*)

Cepharanthin for Tuberculosis.—Cepharanthin, an alkaloid from *Stephania cepharantha*, has been reported by Japanese investigators to be effective in minute doses against tuberculosis. To evaluate these reports, 34 patients with pulmonary tuberculosis were treated with cepharanthin, 0.01 to 0.05 mg., orally every other day or daily every other week for about six months. In 14 relatively mild cases of nonexudative disease there was no evidence that the tuberculosis was influenced by the drug. In 7 moderately severe and 13 severe cases of exudative disease, the drug apparently had an adverse effect with aggravated roentgenographic findings, increased erythrocyte sedimentation rates, greater numbers of tubercle bacilli in the sputum, and increased fever. No patient showed improvement in his general condition and no severely ill patient was saved from death.—*Our experiences upon chemotherapy of lung tuberculosis with "cepharanthin," T. Ebina, I. Kanno, & Yamasaki, Tohoku J. Exper. Med., June, 1949, 50: 267.*—(*L. B. Hobson*)

Bacteriolysis by Actinozyme.—Bacterial agar was prepared by mixing two parts of warm 2 per cent agar in water with one part of a suspension of a 24-hour-old bacterial culture. Cultures of *Staphylococcus albus, S. aureus*, and *E. coli* were most commonly used. The bacterial agar, about as opaque as milk, was allowed to solidify in thin layers. The bacteria were either living or previously killed by heat or chemicals. When the bacterial agar was inoculated with *Actinomyces*, a zone of clearing was formed about the fungi as an actinozyme was liberated into the medium. Microscopically the zone was less marked in plates containing living *Staphylococci* than in those killed with *E. coli*. Immediately surrounding the *Actinomyces* in the former, there was a completely clear zone and beyond that an area of incomplete bacteriolysis. Plates with killed *E. coli* showed only the completely clear zone. A very characteristic halo thus formed in the living *Staphylococci*, perhaps due to a staphylococcal factor which modified the degree and distribution of actinozyme bacteriolysis. With too thick bacterial suspensions, halos of optical origin caused confusion.—*Étude de l'activité bactériolytique des actinomycètes et particulièrement des phénomènes de halo, L. Swertz, Rev. belge de path. et med. exper., September, 1949, 19: 214.*—(*A. T. Laird*)

Production of Viable BCG.—Adequate criteria are still lacking for the standardization of BCG vaccines. They usually have been standardized by the level of attenuation of the culture, the amount of bacterial material in the vaccine, the viability and physiological activity of the bacteria, and so forth. These characteristics probably are of importance in determining the ability of BCG to multiply *in vivo*, and to establish tuberculin allergy and resistance against infection. Most workers

have advocated a rigid adherence to the original technique of Calmette and his associates by which the culture is grown on the surface of a synthetic medium, then removed and ground to obtain a fine bacterial suspension. This technique kills many of the bacilli. It is also well known that the live organisms in the vaccine soon begin to die, and it is recommended that the vaccine be used within a very days following its preparation. The standard BCG vaccine now distributed contains approximately 10^9 bacterial cells per cc.; after 48 hours there are only 10^4 to 10^5 viable cells per cc. These rapidly diminish so that at the average time of use less than 1 per cent of the cells are living. The purpose of the present paper is to show that an active BCG culture containing a large percentage of living cells and with good keeping qualities can be obtained by the use of a Tween-albumin medium. The BCG strain used grew rapidly in Tween-bovine-albumin medium as a submerged growth. To avoid antigenic protein of animal origin, the cultures employed in the experiments were grown in media containing human serum albumin rather than the bovine albumin used in the maintenance medium. After one week's incubation, the medium with human albumin contained a heavy growth of BCG which yielded a macroscopically homogeneous suspension on gentle shaking. Microscopically, small clumps and isolated cells were seen. The bacilli were uniformly acid fast, but the cells were somewhat shorter than those present in a sample of vaccine prepared from the same strain by the conventional technique. Viability studies were done before and after refrigerator storage up to six weeks, using vaccine prepared from an 8-day-old culture in the new medium. No material decrease in the number of viable cells was noted. Under the same conditions the standard or original BCG vaccine often contained less then one-hundredth the initial number of viable cells. Since viability was deemed more important than the yield of bacterial cells, glucose and glycerine were omitted from the medium; they do not increase the number of viable organisms. The cultures obtained consisted predominantly of living cells that remained viable during prolonged storage at temperatures of 4 to 37° C.—*Production of BCG vaccine in liquid medium containing Tween 80 and a soluble fraction of heated human serum: I. Production and viability of culture, R. J. Dubos & F. Fenner, J. Exper. Med., March 1, 1950, 91: 261.*—(*J. S. Woolley*)

Antigenicity of Tween 80 BCG Cultures.—To determine the minimal number of viable units of BCG necessary to render animals allergic to tuberculin, guinea pigs were injected subcutaneously or intracutaneously with various doses of Tween-human-albumin BCG culture. The content of viable units in the culture was determined by plating serial dilutions on Tween-bovine-albumin agar. Definite sensitization was produced with as few as 10 viable units, each consisting of a single bacillus or a clump of bacilli: Only slightly larger doses led to a maximal tuberculin allergy. The same degree of sensitization was achieved by vaccination with 0.1 cc. of either the standard BCG vaccine or of fresh and stored cultures prepared in the new medium. This volume probably contained many more living bacilli than is required to produce maximal sensitization. The local lesions at the site of injection of the Tween medium cultures were more severe than those produced by the standard vaccine, probably because of the much larger number of viable bacilli in the former preparation. Two vaccines, one from a culture of BCG maintained for two years in a Tween-bovine-albumin medium and the other from a culture of standard BCG vaccine, produced lesions of the same severity when comparable dilutions were injected. Guinea pigs were vaccinated intracutaneously with the new vaccines or with standard BCG and then challenged with virulent organisms. The new vaccines gave at least as much protection as the standard BCG under the varied conditions of the experiment. BCG cultures grown in Tween-albumin medium compared well with the cultures prepared by the conventional technique and in some respects were superior.

Besides containing more viable cells, these dispersed cultures were easy to prepare, and obviate the necessity of grinding the bacterial growth.—*Production of BCG vaccine in a liquid medium containing Tween 80 and a soluble fraction of heated human serum. II. Antigenicity of the culture after various periods of storage, F. Fenner and R. Dubos, J. Exper. Med., March 1, 1950, 91: 269.*—(*J. S. Woolley*)

Tubercle Penicillinase.—The authors describe a strain of tubercle bacilli which produces a penicillin-destroying substance. This substance has enzyme-like properties similar to those described for penicillinase from other organisms. It is thermolabile, losing nearly all of its activity after being heated to 60° C. for one hour. It is absorbed when passing through a Seitz filter, is destroyed by agitation, and works best at pH 6.0, being progressively less active at pH levels above and below this optimum.—*The effect of penicillin on the tubercle bacillus: tubercle penicillinase, C. N. Hland & S. Baines, J. Path. & Bact., July, 1949, 61: 329.*—(*H. J. Henderson*)

Modified Hemagglutination Test.—A modification of the Middlebrook and Dubos hemagglutination test appears to be as specific as the original method. It is simple and cheap enough to be used in institutions which cannot prepare the original aqueous extracts or deglycerinate commercial tuberculin. Commercially available Old Tuberculin of four times standard strength, supplied by Lederle Laboratories, is used as the antigen. Of 50 sera from tuberculous patients, 38 were found to have hemagglutinins at a serum dilution of 1:2 or greater. A series of 40 medical students and nurses who received BCG four months previously were tested; 30 showed positive results. In a group of sera from 15 persons having a negative tuberculin skin test, all hemagglutination tests were negative. The clinical significance remains to be determined and is under investigation in a larger series of patients. The data available at present indicate that the test is specific for antibodies against tubercle bacilli.—*A simple modification of the Middlebrook and Dubos hemagglutination test for serum antibodies to products of tubercle bacilli, N. B. Scott & D. T. Smith, J. Lab. & Clin. Med., February, 1950, 35: 303.*—(*F. G. Petrik*)

Leukocyte-tuberculin Reaction.—The inhibition of migration by tuberculin has been described as a specific reaction of leukocytes from tuberculous patients. It is still uncertain whether this inhibition is dependent on factors in the leukocytes or in the plasma of tuberculous persons, and whether it is specific enough to serve as a diagnostic test. To answer these questions, washed leukocytic explants were made from the blood of normal persons and of patients with tuberculosis or other diseases. The explants were incubated with normal or tuberculous serum which had been coagulated with placental extract; Old Tuberculin (OT), purified tuberculin GT, or albumen-free tuberculin AF was added to the extract in various concentrations. Using leukocytes and serum from tuberculous patients, inhibition was obtained in most patients even with tuberculin diluted 1:3,000. Leukocytes from tuberculous patients with serum from normal persons gave a similar response. Leukocytes from normal persons were also inhibited by tuberculin in the presence of serum from tuberculous patients. It seems that the inhibition is a summation of factors present in the serum and cells. Not all of the blood samples from tuberculous patients gave the inhibition reaction; blood from persons with syphilis and infectious hepatitis reacted frequently with high concentrations of OT but less often with lower concentrations. The purified tuberculin preparations were more specific, suggesting that they may be of greater value in diagnostic leukocytic test.—*Spezifische Antigenreaktionen an Leukocyten bei Tuberkulosen, K. Langner, Klin. Wchnschr., March 15, 1950, 28: 177.*—(*L. B. Hobson*)

Plasma Viscosity in Tuberculosis.—Previous reports have suggested that the plasma viscosity is a more accurate index of the activity of tuberculous disease than the erythrocyte

sedimentation rate. Carried out on citrated or oxalated blood in a modified Ostwald viscometer, the test reflected systemic reactions due to nonspecific changes in plasma proteins. In 235 tests carried out on tuberculous patients, the average values for any group of patients were proportional to the severity of the disease. It was also noted that all cases of pleural effusions fell within a narrow range. While viscosity measurements remained in this range, the effusion regularly reappeared after aspiration, and when the value rose above or fell below this level the effusion cleared spontaneously. However, in the case reported, the variations in viscosity seemed rather closely correlated with the mental outlook of the patient. Studies also were carried out on patients with rheumatic fever and rheumatoid arthritis. The values in these diseases also correlated well with the patients' condition and in rheumatic diseases without systemic involvement, such as osteoarthritis, values were normal. In general the data supports the view that this test is more reliable than the erythrocyte sedimentation rate.—*Plasma viscosity in tuberculosis and rheumatic disease, J. Houston, R. Whithington, I. Cowan, & J. Harkness, J. Clin. Investigation, July, 1949, 28: 752.—(S. J. Hadley)*

LABORATORY STUDIES

Toxicity of Beryllium.—Acute beryllium poisoning with pulmonary lesions closely resembling those in man has been produced in animals exposed daily by inhalation to a beryllium sulfate mist. No transition of this response to the lesion of chronic granulomatosis developed after more than three months' exposure. There are indications that inhaled beryllium sulfate produces manifestations other than pulmonary injury and that beryllium gives rise to a complex set of responses. Among these are anemia which resembles the macrocytic type, changes of blood cell constituents, and disturbances of nitrogen metabolism. Sufficient evidence has been adduced, (*1*) in the 4 inhalation studies, (*2*) in control sodium sulfate studies, and (*3*) in studies with pure beryllium metal (intratracheal instillation) that the toxic manifestations observed are the result of the action of beryllium itself and not mainly the result of the associated anions of its acidic salts. The acute toxic responses have been produced at exposure concentrations and by tissue concentrations of beryllium far below those usually encountered in chemical toxicity. Amounts of the order of a few millimicrograms have been found in tissues where changes have been noted (Authors' summary).—*Acute inhalation toxicity of beryllium: 1. Four definitive studies of beryllium sulfate at exposure concentrations of 100, 50, and 1 mg. per cubic meter, H. E. Stokinger, G. F. Sprague III, R. H. Hall, N. J. Ashenburg, J. K. Scott, & L. T. Steadman, Arch. Indust. Hyg. & Occup. Med., April, 1950, 1: 379.—(T. H. Noehren)*

Action of Streptodornase.—Studies have been made of the mode of action of the streptococcal enzyme, desoxyribonuclease (streptodornase). *In vitro*, the viscosity of thymic nucleic acid decreases in direct proportion to the amount of streptodornase added. The action is maximal at 45°C. between pH 7.0 and 8.5. Exposure to the enzyme results in depolymerization of the desoxyribonucleic acids with liberation of acid-soluble phosphorous and nitrogen. Neither penicillin nor salicylates influence the reaction but citrates and heparin inhibit it. When tested on purulent exudates *in vitro* or *in vivo*, similar loss of viscosity and increase in phosphorous and nitrogen are noted. Feulgen-stained preparations of empyema fluids made before and after treatment show a rapid decrease in the amount of extracellular desoxynucleoprotein and in the number of degenerated leukocytes.—*The action of streptococcal desoxyribose nuclease (streptodornase), in vitro and on purulent pleural exudations of patients, S. Sherry, A. Johnson, & W. Tillet, J. Clin. Investigation, September, 1949, 28: 1094.—(S. Hadley)*

Lung Blood Volume.—By injecting the dye T-1824 into the pulmonary artery and measuring the concentration of dye in con-

secutive samples of blood from the femoral artery, the authors determined the mean circulation time in a group of 13 normal men. A value of 10.2 ± 1.6 seconds was obtained. Then using the cardiac output as determined by the direct Fick principle and Stewart's formula

$$[\text{cardiac output (cc./min.)} \times \text{mean circulation time (sec.)}]$$

the volume of blood in the pulmonary vessels, left heart, aorta, and certain larger systemic arteries was found to be 1160 ± 246 cc. or 19.5 per cent of the total blood volume. This represents a much more accurate value than the older and cruder methods were able to determine.—*Studies of pulmonary circulation. I. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs of normal individuals, R. Ebert, C. Borden, H. Wells, & R. Wilson, J. Clin. Investigation, September, 1949, 28: 1134.*—(*S. Hadley*)

Adrenaline and Anoxic Hyperventilation.—A study has been made of the role of adrenaline in the respiratory response of dogs to hypoxemia produced by rebreathing room air when the expired carbon dioxide is removed by soda lime. Removal of the adrenal glands reduced the mean maximum ventilation of 7 dogs from 11.5 liters per minute to 7.0 liters per minute, and injection of adrenaline partially restored this reduction (mean maximum ventilation of 8.8 liters per minute). No significant changes were noted in the respiratory responses to hypoxemia of a group of 6 dogs exposed to comparable surgical and experimental procedures. Two hypothetical explanations are advanced for the mechanism of the effect of adrenaline on respiratory response to hypoxemia. These are: (*1*) the effect might be secondary to a general increase in metabolism; (*2*) there may be a central stimulatory effect of adrenaline on respiration. (Authors' summary)—*Role of adrenaline in respiratory response to hypoxemia, R. W. Stacy & D. D. Demunbrun, Am. J. Physiol., April, 1950, 161: 51.*—(*G. C. Leiner*)

Relief of Bronchospasm.—Six sympathomimetic amines were tested for their effectiveness in relieving bronchospasm by evaluating the protection afforded patients against dyspnea and bronchospasm caused by repeated intravenous administration of histamine and methacholine. This was measured by changes in vital capacity. Of the solutions used for nebulization, vaponephrin 2.25 per cent was slightly better than either isuprel, 1:200, or epinephrine, 1:100. Six inhalations of isuprel, 1:100, were equal to 0.5 cc. of epinephrine subcutaneously. Doses of 0.5 cc. of 1:1,000 epinephrine or 1:5,000 isuprel given subcutaneously were the best of the agents tested but often gave undesirable side effects. Neosynephrine by any route and isuprel sublingually were of little value. Ephedrine and a new compound, orthoxine, when taken by mouth, resulted in fair protection if time were allowed for absorption.—*Evaluation of therapeutic substances employed for the relief of bronchospasm: V. Adrenergic agents, E. Bresnick, J. Beakey, L. Levinson, & M. Segal, J. Clin. Investigation, September, 1949, 28: 1182.*—(*S. Hadley*)

Aminophylline for Bronchospasm.—Various routes of administering aminophylline to patients have been studied to evaluate their effectiveness in protecting against histamine-induced bronchospasm as measured by changes in vital capacity. Rectal administration of 0.5 gm. in 15 cc. of water is equal or superior to intravenous administration of the drug if 45 to 60 minutes delay is not inconvenient. Intramuscularly the drug is relatively ineffective when compared with equal amounts given by vein. Given orally or by aerosol, aminophylline is ineffective. Similar results are obtained when each route is tried on the same person. In general the effect of aminophylline is more prolonged than that of the sympathomimetic drugs, usually continuing for three or more hours.—*Evaluation of therapeutic substances employed for the relief of bronchospasm. VI. Aminophylline, M. Segal, L. Levinson, J. Beakey, & E. Bresnick,*

J. Clin. Investigation, September, 1949, 28: 1190.—(S. Hadley).

Pulmonary Retention of Particles.—It has been stated that inhaled particles measuring 1 to 5 μ in diameter are retained in the human lung; those measuring less than 1 μ are only partially retained. Fewer particles are retained during oral than during nasal breathing. Almost all particulate matter 5 to 10 μ in diameter is retained in the nose and does not penetrate to the alvoli. Particles 1 μ long are filtered out by the nose to a negligible extent, suggesting that alveolar deposition is greater when the length is 1 to 2 μ. Retention of respired particles occurs during both inspiration and expiration and decreases as the respiratory rate increases. Nasal retention decreases as the air flow increases if the particles are smaller than 2 μ. With particles of this size, the greater over-all retention during slow breathing is due to increased alveolar deposition because more time is allowed for sedimentation. The respiratory pattern determines both the site of deposition and the percentage retained only when the particles are between 1 and 5 μ in diameter. To test these statements, China clay dusts were inhaled. The particles for each experiment were uniform in size with limits of about 1 μ and in different tests ranged from 0.24 to 10 μ in diameter. The amount of dust retained was calculated from the content of inspired and expired air, the latter being collected serially in fractions representing that reaching the upper respiratory tract, the lower air passages, and the alveoli. The depth reached by each fraction was determined by its carbon dioxide content as compared to that of alveolar air. The results confirmed the previous statements and allowed alveolar deposition to be distinguished from tracheobronchial deposition. It seems that particles larger than 10 μ have little significance in the pathogenesis of dust diseases or in respiratory infection with tuberculosis. Particles smaller than 0.24 μ are unimportant in the transmission of tuberculosis, but may be significant in producing dust diseases. It is probable that retention of these very small particles is increased by Brownian movement.—*Influence of particle size upon the retention of particulate matter in the human lung, J. H. Brown, K. M. Cook, F. G. Ney, & Theodore Hatch, Am. J. Pub. Health, April, 1950, 40: 450.—(Max B. Lurie)*

PUBLIC HEALTH AND EPIDEMIOLOGY

BCG Vaccine.—In evaluating BCG vaccination efficacy, the following considerations must be kept in mind: (*1*) The literature must be studied closely to determine whether studies have been well controlled, else they lose their value. (*2*) Care must be taken that one does not draw conclusions from reports of observations on groups that are too small to warrant generalization. (*3*) BCG vaccine has been used on humans since 1921, yet we do not know whether it is effective and, if so, how effective. (*4*) The theory that a positive tuberculin reaction predisposes to reinfection is not compatible with a belief in BCG vaccination. The theory that the development of a positive tuberculin reaction indicates some degree of resistance to reinfection does explain the belief that BCG vaccination results in increased resistance. (*5*) The tuberculin reaction is a valuable aid in the diagnosis of tuberculosis, an aid which is lost when the vaccinated individual is changed from a nonreactor to a reactor to tuberculin. (*6*) A number of bacteriological and immunological problems remain to be solved before many of the questions regarding BCG vaccination can be answered. These problems include standardization and stabilization of the antigenic potency of the vaccine and the response of the individual in terms of protective immunity, if any. (*7*) The Trudeau Society considers BCG vaccine, properly prepared and administered, to be harmless but points out that further studies are needed before the degree of protection can be predicted. (*8*) The approved general control measures which have been found to be effective must be continued until further proof of efficacy of BCG vaccination is available (Author's summary). —*Shall we accept or reject BCG vaccine? R. L. Todd, Lancet, April, 1950, 1: 141.—(H. J. Henderson)*

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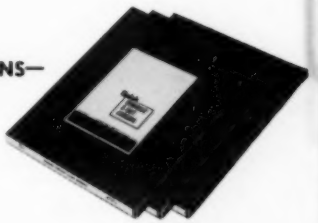

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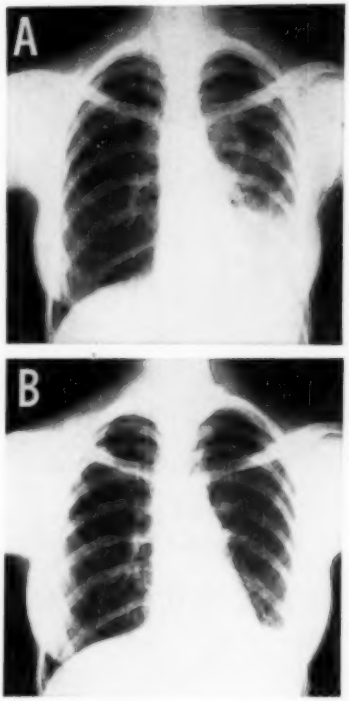

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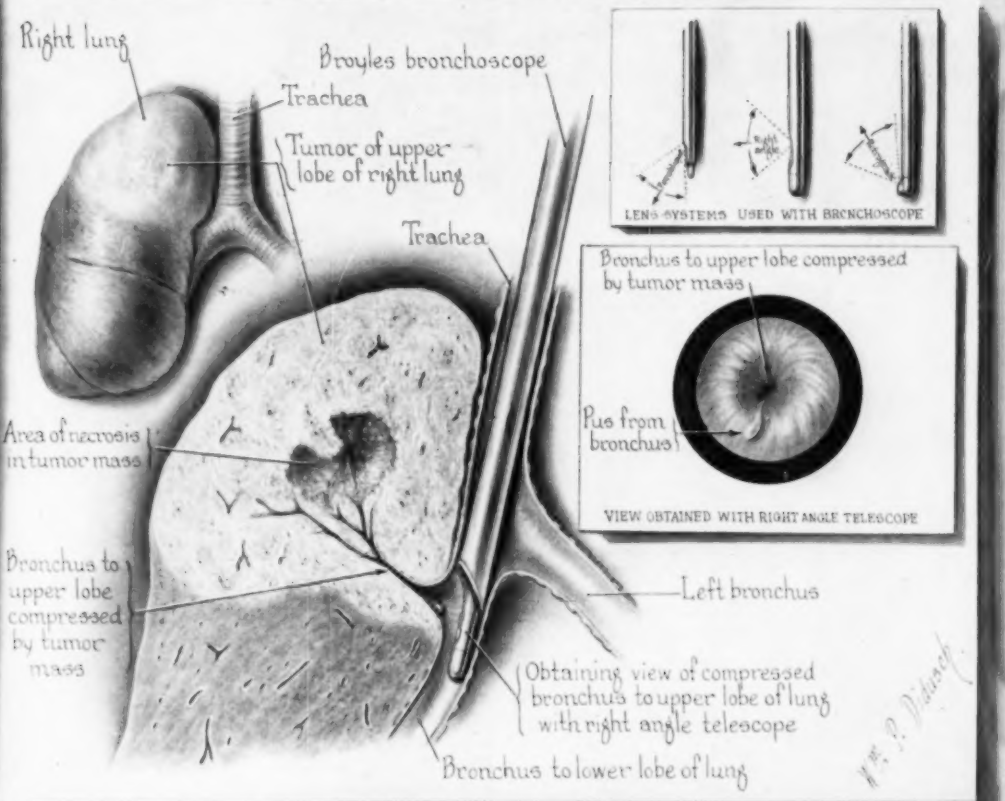
Right lung
Broyles bronchoscope
Trachea
Tumor of upper lobe of right lung
Trachea
Area of necrosis in tumor mass
Bronchus to upper lobe compressed by tumor mass
Left bronchus
Obtaining view of compressed bronchus to upper lobe of lung with right angle telescope
Bronchus to lower lobe of lung
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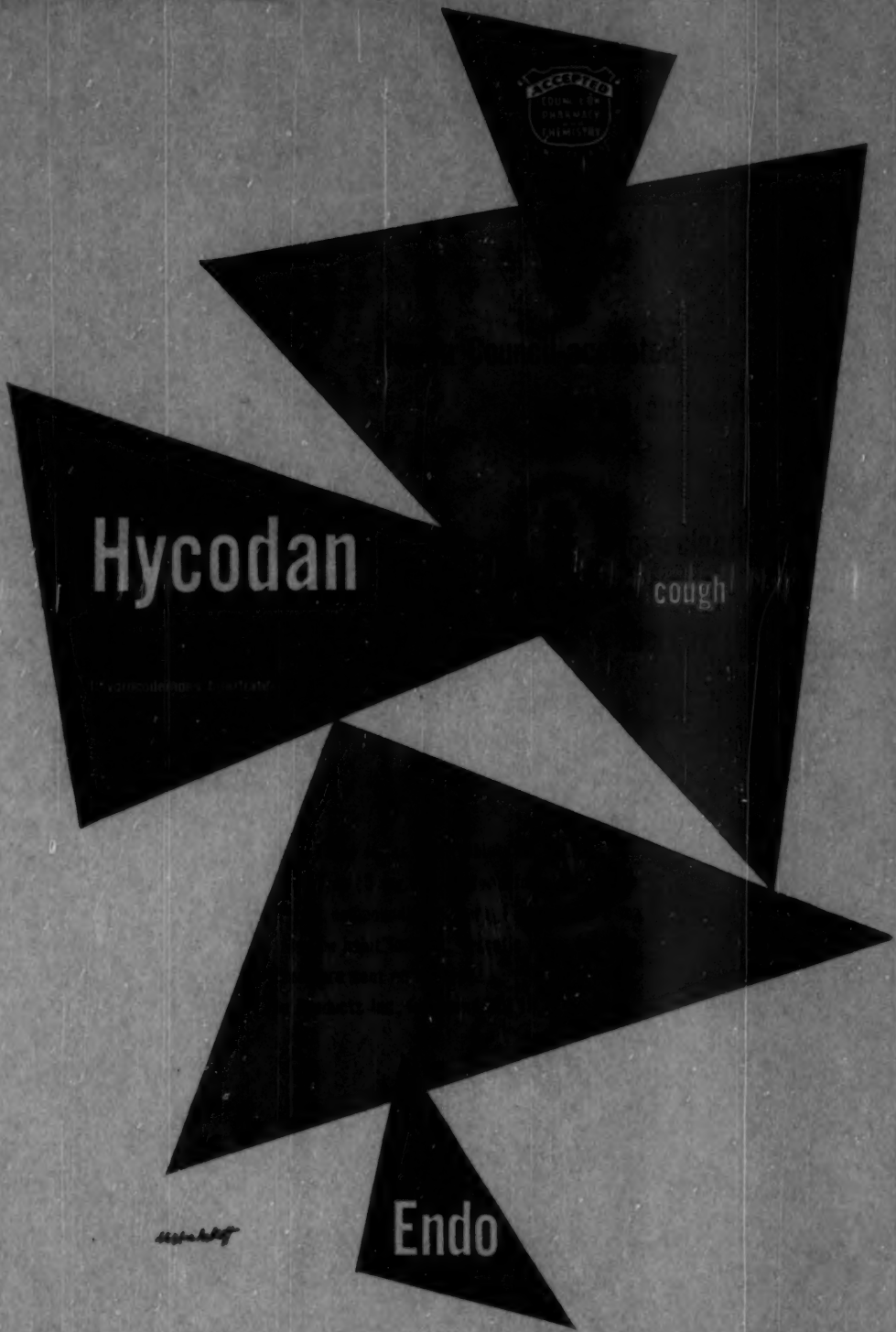
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